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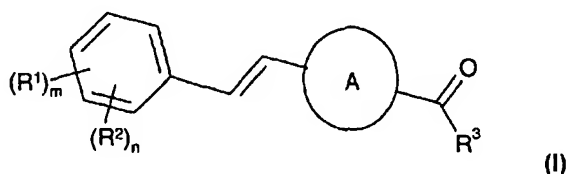
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(54) Title: VINYL PHENYL DERIVATIVES AS GLK ACTIVATORS



(57) Abstract: The invention related to novel compounds of Formula (I) or a salt, solvate or prodrug thereof, wherein A, R¹, R², R³, n and m are as described in the specification, useful in the treatment of formula (I) a disease or condition mediated through glucokinase (GLK), such as type 2 diabetes. The invention also relates to methods for preparing compounds of formula (I) and their use as medicaments in the treatment of diseases mediated by glucokinase.

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VINYL PHENYL DERIVATIVES AS GLK ACTIVATORS

The present invention relates to compounds which activate glucokinase (GLK), leading to a decreased glucose threshold for insulin secretion. In addition the compounds are
5 predicted to lower blood glucose by increasing hepatic glucose uptake. Such compounds may have utility in the treatment of Type 2 diabetes and obesity. The invention also relates to pharmaceutical compositions comprising a compound of the invention, and use of such a compound in the conditions described above.

In the pancreatic β -cell and liver parenchymal cells the main plasma membrane
10 glucose transporter is GLUT2. Under physiological glucose concentrations the rate at which GLUT2 transports glucose across the membrane is not rate limiting to the overall rate of glucose uptake in these cells. The rate of glucose uptake is limited by the rate of phosphorylation of glucose to glucose-6-phosphate (G-6-P) which is catalysed by glucokinase (GLK) [1]. GLK has a high (6-10mM) K_m for glucose and is not inhibited by physiological
15 concentrations of G-6-P [1]. GLK expression is limited to a few tissues and cell types, most notably pancreatic β -cells and liver cells (hepatocytes) [1]. In these cells GLK activity is rate limiting for glucose utilisation and therefore regulates the extent of glucose induced insulin secretion and hepatic glycogen synthesis. These processes are critical in the maintenance of whole body glucose homeostasis and both are dysfunctional in diabetes [2].

20 In one sub-type of diabetes, Type 2 maturity-onset diabetes of the young (MODY-2), the diabetes is caused by GLK loss of function mutations [3, 4]. Hyperglycaemia in MODY-2 patients results from defective glucose utilisation in both the pancreas and liver [5]. Defective glucose utilisation in the pancreas of MODY-2 patients results in a raised threshold for glucose stimulated insulin secretion. Conversely, rare activating mutations of GLK reduce
25 this threshold resulting in familial hyperinsulinism [6, 7]. In addition to the reduced GLK activity observed in MODY-2 diabetics, hepatic glucokinase activity is also decreased in type 2 diabetics [8]. Importantly, global or liver selective overexpression of GLK prevents or reverses the development of the diabetic phenotype in both dietary and genetic models of the disease [9-12]. Moreover, acute treatment of type 2 diabetics with fructose improves glucose
30 tolerance through stimulation of hepatic glucose utilisation [13]. This effect is believed to be mediated through a fructose induced increase in cytosolic GLK activity in the hepatocyte by the mechanism described below [13].

- 2 -

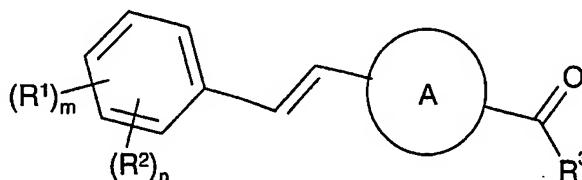
Hepatic GLK activity is inhibited through association with GLK regulatory protein (GLKRP). The GLK/GLKRP complex is stabilised by fructose-6-phosphate (F6P) binding to the GLKRP and destabilised by displacement of this sugar phosphate by fructose-1-phosphate (F1P). F1P is generated by fructokinase mediated phosphorylation of dietary fructose.

5 Consequently, GLK/GLKRP complex integrity and hepatic GLK activity is regulated in a nutritionally dependent manner as F6P is elevated in the post-absorptive state whereas F1P predominates in the post-prandial state. In contrast to the hepatocyte, the pancreatic β -cell expresses GLK in the absence of GLKRP. Therefore, β -cell GLK activity is regulated exclusively by the availability of its substrate, glucose. Small molecules may activate GLK
10 either directly or through destabilising the GLK/GLKRP complex. The former class of compounds are predicted to stimulate glucose utilisation in both the liver and the pancreas whereas the latter are predicted to act exclusively in the liver. However, compounds with either profile are predicted to be of therapeutic benefit in treating Type 2 diabetes as this disease is characterised by defective glucose utilisation in both tissues.

15 In WO0058293 and WO 01/44216 (Roche), a series of benzylcarbamoyl compounds are described as glucokinase activators. The mechanism by which such compounds activate GLK is assessed by measuring the direct effect of such compounds in an assay in which GLK activity is linked to NADH production, which in turn is measured optically - see details of the *in vitro* assay described in Example A.

20 In WO9622282/93/94/95 and WO9749707/8 are disclosed a number of intermediates used in the preparation of compounds useful as vasopressin agents which are related to those disclosed in the present invention. Related compounds are also disclosed in WO9641795 and JP8143565 (vasopressin antagonism), in JP8301760 (skin damage prevention) and in EP619116 (osetopathy).

25 We present as a feature of the invention the use of a compound of Formula (I) or a salt, pro-drug or solvate thereof, in the preparation of a medicament for use in the treatment or prevention of a disease or medical condition mediated through GLK:



Formula (I)

- 3 -

wherein

A is heteroaryl;

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;

5 and $n + m > 0$;

each R^1 is independently selected from OH, $-(CH_2)_{1-4}OH$, $-CH_3-aF_a$, $-(CH_2)_{1-4}CH_3-aF_a$, $-OCH_3-aF_a$, halo, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, NO_2 , NH_2 , $-NH-C_{1-4}alkyl$, $-N-di-(C_{1-4}alkyl)$, CN, formyl, phenyl or heterocyclyl optionally substituted by $C_{1-6}alkyl$;

10 each R^2 is the group $Y-X-$

wherein each X is a linker independently selected from:

$-Z-$, $-O-Z-$, $-O-Z-O-Z-$, $-C(O)O-Z-$, $-OC(O)-Z-$, $-S-Z-$, $-SO-Z-$, $-SO_2-Z-$, $-N(R^7)-Z-$, $-N(R^7)SO_2-Z-$, $-SO_2N(R^7)-Z-$, $-(CH_2)_{1-4}-$, $-CH=CH-Z-$, $-C\equiv C-Z-$, $-N(R^7)CO-Z-$, $-CON(R^7)-Z-$, $-C(O)N(R^7)S(O)_2-Z-$, $-S(O)_2N(R^7)C(O)-Z-$, $-C(O)-Z-$ or a direct

15 bond;

each Z is independently a direct bond, $C_{2-6}alkenylene$ or a group of the formula

$-(CH_2)_p-C(R^7)_2-(CH_2)_q-$;

each Y is independently selected from aryl- Z^1- , heterocyclyl- Z^1- , $C_{3-7}cycloalkyl-Z^1-$,

$C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $-(CH_2)_{1-4}CH_3-aF_a$ or $-CH(OH)CH_3-aF_a$; wherein

20 each Y is independently optionally substituted by up to 3 R^4 groups;

each R^4 is independently selected from halo, $-CH_3-aF_a$, CN, NO_2 , NH_2 , $C_{1-6}alkyl$, $-OC_{1-6}alkyl$, $-COOH$, $-C(O)OC_{1-6}alkyl$, OH or phenyl optionally substituted by $C_{1-6}alkyl$ or $-C(O)OC_{1-6}alkyl$,

or R^5-X^1- , where X^1 is independently as defined in X above and R^5 is

25 selected from hydrogen, $C_{1-6}alkyl$, $-CH_3-aF_a$, phenyl, naphthyl, heterocyclyl

or $C_{3-7}cycloalkyl$; and R^5 is optionally substituted by halo, $C_{1-6}alkyl$,

$-CH_3-aF_a$, CN, NO_2 , NH_2 , $COOH$, or $-C(O)OC_{1-6}alkyl$,

wherein each phenyl, naphthyl or heterocyclyl ring in R^5 is optionally

substituted by halo, CH_3-aF_a , CN, NO_2 , NH_2 , $C_{1-6}alkyl$, $-OC_{1-6}alkyl$, $COOH$,

30 $-C(O)OC_{1-6}alkyl$ or OH;

each Z^1 is independently a direct bond, $C_{2-6}alkenylene$ or a group of the formula

$-(CH_2)_p-C(R^6)_2-(CH_2)_q-$;

- 4 -

R^3 is selected from OH, $-O-C_{1-6}$ alkyl or NHR^6 ;

R^6 is selected from hydrogen, C_{1-6} alkyl, $-O-C_{1-6}$ alkyl, $-SO_2C_{1-6}$ alkyl, $-(CH_2)_{0-3}OH$;

R^7 is independently selected from hydrogen, C_{1-6} alkyl or $-C_{2-4}$ alkyl- $O-C_{1-4}$ alkyl;

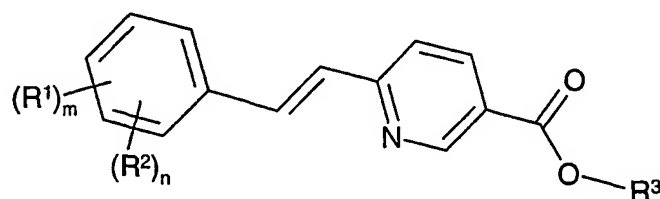
each a is independently 1, 2 or 3;

5 p is an integer between 0 and 2;

q is an integer between 0 and 2;

and $p + q < 4$.

According to a further feature of the invention there is provided the use of a compound of Formula (Ia) or a salt, pro-drug or solvate thereof, in the preparation of a medicament for
10 use in the treatment or prevention of a disease or medical condition mediated through GLK:



Formula (Ia)

wherein

m is 0, 1 or 2;

15 n is 0, 1, 2, 3 or 4;

and $n + m > 0$;

each R^1 is independently selected from OH, $(CH_2)_{1-4}OH$, CH_3-aF_a , $(CH_2)_{1-4}CH_3-aF_a$,

OCH_3-aF_a , halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, NO_2 , NH_2 , CN, phenyl or a heterocyclyl optionally substituted by C_{1-6} alkyl;

20 each R^2 is the group $Y-X-$

wherein each X is a linker independently selected from

$-O(CH_2)_{0-3}-$, $-(CH_2)_{0-3}O-$, $-C(O)O(CH_2)_{0-3}-$, $-S(CH_2)_{0-3}-$, $-SO(CH_2)_{0-3}-$,
 $-SO_2(CH_2)_{0-3}-$, $-NHSO_2$, $-SO_2NH-$, $-(CH_2)_{1-4}-$, $-CH=CH(CH_2)_{0-2}-$, $-C\equiv C(CH_2)_{0-2}-$,
 $-NHCO-$, $-CONH-$;

25 each Y is independently selected from phenyl $(CH_2)_{0-2}$, naphthyl $(CH_2)_{0-2}$,

heterocyclyl $(CH_2)_{0-2}$, C_{3-7} cycloalkyl $(CH_2)_{0-2}$, C_{1-6} alkyl, OC_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or $CH(OH)CH_3-aF_a$; wherein each Y is independently optionally substituted by one or more R^4 groups;

- 5 -

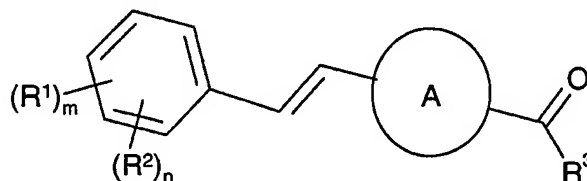
- each R^4 is independently selected from halo, $CH_{3-a}F_a$, $OCH_{3-a}F_a$, CN, NO_2 , NH_2 , $C_{1-6}alkyl$, $OC_{1-6}alkyl$, $COOH$, $(CH_2)_{0-3}COOH$, $O(CH_2)_{0-3}COOH$, $C(O)OC_{1-6}alkyl$, $C_{1-6}alkylC(O)OC_{1-6}alkyl$, CO-phenyl, $CONH_2$, CONH-phenyl, SO_2NH_2 , $SO_2C_{1-6}alkyl$, OH, or phenyl optionally substituted by one or more R^5 groups where R^5 is selected from hydrogen, $C_{1-6}alkyl$ or $C(O)OC_{1-6}alkyl$.

each a is independently 1, 2 or 3;

R^3 is selected from hydrogen, $C_{1-6}alkyl$ or NHR^6 ;

R^6 is selected from hydrogen, $C_{1-6}alkyl$, $OC_{1-6}alkyl$, $SO_2C_{1-6}alkyl$, $(CH_2)_{0-3}OH$.

- 10 According to a further feature of the invention there is provide a compound of Formula (Ib) or a salt, solvate or pro-drug thereof;



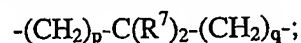
Formula (Ib)

wherein

- 15 A is heteroaryl;
 m is 0, 1 or 2;
 n is 0, 1, 2, 3 or 4;
and $n + m > 0$;
each R^1 is independently selected from OH, $-(CH_2)_{1-4}OH$, $-CH_{3-a}F_a$, $-(CH_2)_{1-4}CH_{3-a}F_a$, $-OCH_{3-a}F_a$, halo, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, NO_2 , NH_2 , $-NH-C_{1-4}alkyl$, $-N-di-(C_{1-4}alkyl)$, CN, formyl, phenyl or heterocyclyl optionally substituted by $C_{1-6}alkyl$;
20 each R^2 is the group Y-X-
wherein each X is a linker independently selected from:
25 -Z-, -O-Z-, -O-Z-O-Z-, -C(O)O-Z-, -OC(O)-Z-, -S-Z-, -SO-Z-, -SO₂-Z-, -N(R^7)-Z-, -N(R^7)SO₂-Z-, -SO₂N(R^7)-Z-, $-(CH_2)_{1-4}-$, $-CH=CH-Z-$, $-C\equiv C-Z-$, $-N(R^7)CO-Z-$, $-CON(R^7)-Z-$, $-C(O)N(R^7)S(O)_2-Z-$, $-S(O)_2N(R^7)C(O)-Z-$, $-C(O)-Z-$ or a direct bond;

- 6 -

each **Z** is independently a direct bond, C₂₋₆alkenylene or a group of the formula



each **Y** is independently selected from aryl-Z¹-, heterocyclyl-Z¹-, C₃₋₇cycloalkyl-Z¹-,

C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, $-(\text{CH}_2)_{1-4}\text{CH}_3\text{-aF}_a$ or $-\text{CH}(\text{OH})\text{CH}_3\text{-aF}_a$; wherein

5 each **Y** is independently optionally substituted by up to 3 **R**⁴ groups;

each **R**⁴ is independently selected from halo, $-\text{CH}_3\text{-aF}_a$, CN, NO₂, NH₂, C₁₋₆alkyl,

$-\text{OC}_{1-6}\text{alkyl}$, $-\text{COOH}$, $-\text{C}(\text{O})\text{OC}_{1-6}\text{alkyl}$, OH or phenyl optionally substituted

by C₁₋₆alkyl or $-\text{C}(\text{O})\text{OC}_{1-6}\text{alkyl}$,

or **R**⁵-**X**¹-, where **X**¹ is independently as defined in **X** above and **R**⁵ is

10 selected from hydrogen, C₁₋₆alkyl, $-\text{CH}_3\text{-aF}_a$, phenyl, naphthyl, heterocyclyl

or C₃₋₇cycloalkyl; and **R**⁵ is optionally substituted by halo, C₁₋₆alkyl,

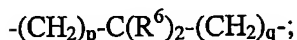
$-\text{CH}_3\text{-aF}_a$, CN, NO₂, NH₂, COOH, or $-\text{C}(\text{O})\text{OC}_{1-6}\text{alkyl}$,

wherein each phenyl, naphthyl or heterocyclyl ring in **R**⁵ is optionally

substituted by halo, $\text{CH}_3\text{-aF}_a$, CN, NO₂, NH₂, C₁₋₆alkyl, $-\text{OC}_{1-6}\text{alkyl}$, COOH,

15 $-\text{C}(\text{O})\text{OC}_{1-6}\text{alkyl}$ or OH;

each **Z**¹ is independently a direct bond, C₂₋₆alkenylene or a group of the formula



R³ is selected from OH, $-\text{O}-\text{C}_{1-6}\text{alkyl}$ or NHR^6 ;

R⁶ is selected from hydrogen, C₁₋₆alkyl, $-\text{O}-\text{C}_{1-6}\text{alkyl}$, $-\text{SO}_2\text{C}_{1-6}\text{alkyl}$, $-(\text{CH}_2)_{0-3}\text{OH}$;

20 **R**⁷ is independently selected from hydrogen, C₁₋₆alkyl or $-\text{C}_{2-4}\text{alkyl}-\text{O}-\text{C}_{1-4}\text{alkyl}$;

each **a** is independently 1, 2 or 3;

p is an integer between 0 and 2;

q is an integer between 0 and 2;

and **p** + **q** < 4.

25 with the proviso that:

(i) when **m** is 1 or 2 and **n** is 0, **R**³ is OH or $-\text{O}-\text{C}_{1-6}\text{alkyl}$, then **R**¹ is other than OH, CN, halo, methyl, amino or nitro;

(ii) when **m** = 0, **n** = 1, **X** is $-\text{O}-$, $-\text{O}-\text{C}(\text{O})-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O}_2)-$, $-\text{N}(\text{CH}_3)-$, $-\text{N}(\text{CH}_3)-\text{CH}_2-$ or $-\text{C}(\text{O})-\text{NH}-$, **R**³ is OH or $-\text{O}-\text{C}_{1-6}\text{alkyl}$, then **Y** cannot be C₁₋₆alkyl or C₁₋₆alkyl substituted

30 by C₁₋₆alkyl;

- 7 -

- (iii) when m is 0 or m is 1 and R^1 is NO_2 , R^3 is OH or $-O-C_{1-6}alkyl$, then when n is 2 $(R^2)_n$ cannot be di- $C_{1-6}alkyl-O-$ or $C_{1-6}alkyl-O-C_{1-6}alkenyl-O-$ and when n is 3 $(R^2)_n$ cannot be tri- $C_{1-6}alkyl-O-$;
- (iv) when A is pyridyl, m is 0 or m is 1 and R^1 is halo, n is 1 and R^2 is phenyl, phenyl- CH_2-O- or pyridyl-NH-, then R^3 cannot be OH or $-O-C_{1-6}alkyl$; and
- (v) when A is pyridyl, R^3 is OH, m is 0, n is 2 and one of the R^2 groups is phenyl- CH_2-O- , then the other R^2 group must be other than CH_3-S- or CH_3-SO_2- .

According to a further feature of the invention there is provided a compound of Formula (Ib) or salt, solvate of pro-drug thereof,

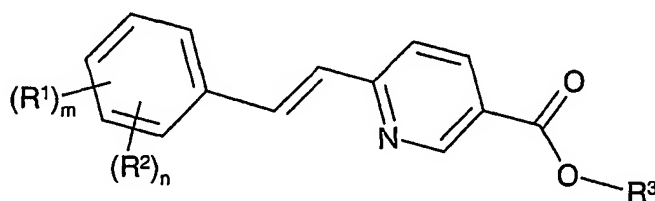
10 wherein A is pyridyl

with the proviso that:

- (i) when m is 1 or 2 and n is 0 then R^1 is other than halo, methyl, amino or nitro;
- (ii) when $m=0$, $n=1$, X is $-O-$, $-S-$, $-S(O)-$, $-S(O_2)-$, $-N(CH_3)-$, or $-N(CH_3)-CH_2-$, R^3 is OH or $-O-C_{1-6}alkyl$, then Y cannot be methyl;
- 15 (iii) when R^3 is OH, m is 0, n is 2 and one of the R^2 groups is phenyl- CH_2-O- , then the other R^2 group must be other than CH_3-S- or CH_3-SO_2- ; and
- (iv) when m is 0 or m is 1 and R^1 is halo, n is 1 and R^2 is phenyl, phenyl- CH_2-O- or pyridyl-NH-, then R^3 cannot be OH or $-O-C_{1-6}alkyl$;

According to a further feature of the invention there is provided a compound of

20 Formula (Ic) or a salt, solvate or pro-drug thereof;



Formula (Ic)

wherein

- m is 0, 1 or 2;
- 25 n is 0, 1, 2, 3 or 4;
- and $n + m > 0$;
- each R^1 is independently selected from OH, $(CH_2)_{1-4}OH$, $CH_{3-a}F_a$, $(CH_2)_{1-4}CH_{3-a}F_a$, $OCH_{3-a}F_a$, halo, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, NO_2 , NH_2 , CN, phenyl or a heterocyclyl optionally substituted by $C_{1-6}alkyl$;

- 8 -

each R^2 is the group $Y-X$ -

wherein each X is a linker independently selected from

$-O(CH_2)_{0-3}-$, $-(CH_2)_{0-3}O-$, $-C(O)O(CH_2)_{0-3}-$, $-S(CH_2)_{0-3}-$, $-SO(CH_2)_{0-3}-$,
 $-SO_2(CH_2)_{0-3}-$, $-NHSO_2$, $-SO_2NH-$, $-(CH_2)_{1-4}-$, $-CH=CH(CH_2)_{0-2}-$, $-C\equiv C(CH_2)_{0-2}-$,
 5 $-NHCO-$, $-CONH-$;

each Y is independently selected from phenyl $(CH_2)_{0-2}$, naphthyl $(CH_2)_{0-2}$,
 heterocyclyl $(CH_2)_{0-2}$, C_{3-7} cycloalkyl $(CH_2)_{0-2}$, C_{1-6} alkyl, OC_{1-6} alkyl, C_{2-6} alkenyl,
 C_{2-6} alkynyl, or $CH(OH)CH_3$ - F_a ; wherein each Y is independently optionally
 substituted by one or more R^4 groups;

10 each R^4 is independently selected from halo, CH_3 - F_a , OCH_3 - F_a , CN, NO_2 , NH_2 ,
 C_{1-6} alkyl, OC_{1-6} alkyl, COOH, $(CH_2)_{0-3}COOH$, $O(CH_2)_{0-3}COOH$,
 $C(O)OC_{1-6}$ alkyl, C_{1-6} alkyl $C(O)OC_{1-6}$ alkyl, CO-phenyl, $CONH_2$,
 $CONH$ -phenyl, SO_2NH_2 , SO_2C_{1-6} alkyl, OH, or phenyl optionally substituted
 by one or more R^5 groups where R^5 is selected from hydrogen, C_{1-6} alkyl or
 15 $C(O)OC_{1-6}$ alkyl.

each a is independently 1, 2 or 3;

R^3 is selected from hydrogen, C_{1-6} alkyl or NHR^6 ;

R^6 is selected from hydrogen, C_{1-6} alkyl, OC_{1-6} alkyl, SO_2C_{1-6} alkyl, $(CH_2)_{0-3}OH$;

with the proviso that:

- 20 (i) when R^3 is H, m is 0, n is 2 and one of the R^2 groups is phenyl- CH_2 -O-, then the other R^2
 group must be other than CH_3 -S- or CH_3 - SO_2 -; and
 (ii) when R^3 is H, m is 1, n is 1 and R^2 is phenyl- CH_2 -O-, then R^1 must be other than halo.

Compounds of the invention may form salts which are within the ambit of the invention.

Pharmaceutically acceptable salts are preferred although other salts may be useful in, for

25 example, isolating or purifying compounds.

The term "aryl" refers to phenyl, naphthyl or a partially saturated bicyclic
 carbocyclic ring containing between 8 and 12 carbon atoms, preferably between 8 and 10
 carbon atoms. Example of partially saturated bicyclic carbocyclic ring include:

1,2,3,4-tetrahydronaphthyl, indanyl, indenyl, 1,2,4a,5,8,8a-hexahydronaphthyl or 1,3a-

30 dihydropentalene.

The term "halo" includes fluoro, chloro, bromo and iodo; preferably chloro, bromo
 and fluoro; most preferably fluoro.

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The expression “-CH_{3-a}F_a” wherein a is an integer between 1 and 3 refers to a methyl group in which 1, 2 or all 3 hydrogen are replaced by a fluorine atom. Examples include: trifluoromethyl, difluoromethyl and fluoromethylene. An analogous notation is used with reference to the group -(CH₂)₁₋₄CH_{3-a}F_a, examples include: 2,2-difluoroethyl and
 5 3,3,3-trifluoropropyl.

In this specification the term “alkyl” includes both straight and branched chain alkyl groups. For example, “C₁₋₄alkyl” includes propyl, isopropyl and *tert*-butyl.

The term “heteroaryl” refers to a monocyclic aromatic heterocyclic ring containing between 5-6 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen,
 10 which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH₂- group can optionally be replaced by a -C(O)- and sulphur atoms in a heterocyclic ring may be oxidised to S(O) or S(O)₂ groups. Examples of “heteroaryl” include: thiazolidinyl, pyrrolidinyl, pyrrolinyl, 2-oxopyrrolidinyl, 2,5-dioxopyrrolidinyl, 1,1-dioxotetrahydrothienyl, 2,4-dioxoimidazolidinyl, 2-oxo-1,3,4-(4-triazolyl),
 15 2-oxo-oxazolidinyl, 5,6-dihydrouacilyl, 1,2,4-oxadiazolyl, 4-oxothiazolidinyl, morpholinyl, furanyl, 2-oxotetrahydrofuranlyl, tetrahydrofuranlyl, thienyl, isoxazolyl, tetrahydropyranlyl, piperidyl, piperazinyl, thiomorpholinyl, 1,1-dioxothiomorpholinyl, tetrahydropyranlyl, 1,3-dioxolanyl, homopiperazinyl, isoxazolyl, imidazolyl, pyrrolyl, thiazolyl, thiadiazolyl, isothiazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl, pyranlyl, pyrimidyl,
 20 pyrazinyl, pyridazinyl, pyridyl, 4-oxo-pyridinyl, 1,1-dioxotetrahydrothienyl. Preferably “heteroaryl” is selected from: pyridyl, pyrimidinyl, pyrazinyl, furanyl or thiazolyl.

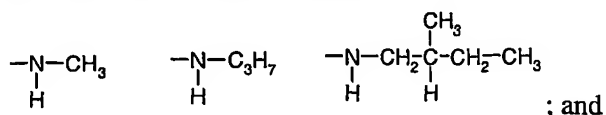
The term “heterocyclyl” is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 3-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked,
 25 wherein a -CH₂- group can optionally be replaced by a -C(O)- and sulphur atoms in a heterocyclic ring may be oxidised to S(O) or S(O)₂ groups. Preferably a “heterocyclyl” is a saturated, partially saturated or unsaturated, mono or bicyclic ring (preferably monocyclic) containing 5 or 6 atoms of which 1 to 3 atoms are nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH₂- group can optionally
 30 be replaced by a -C(O)- or sulphur atoms in a heterocyclic ring may be oxidised to S(O) or S(O)₂ groups. Examples and suitable values of the term “heterocyclyl” are thiazolidinyl, pyrrolidinyl, pyrrolinyl, 2-pyrrolidinyl, 2,5-dioxopyrrolidinyl, 2-benzoxazolinonyl, 1,1-

- 10 -

dioxotetrahydrothienyl, 2,4-dioxoimidazolidinyl, 2-oxo-1,3,4-(4-triazolynyl),
 2-oxazolidinonyl, 5,6-dihydrouracilyl, 1,3-benzodioxolyl, 1,2,4-oxadiazolyl, 2-
 azabicyclo[2.2.1]heptyl, 4-thiazolidonyl, morpholino, furanyl, 2-oxotetrahydrofuranyl,
 tetrahydrofuranyl, 2,3-dihydrobenzofuranyl, benzothienyl, isoxazolyl, tetrahydropyranyl,
 5 piperidyl, 1-oxo-1,3-dihydroisoindolyl, piperazinyl, thiomorpholino,
 1,1-dioxothiomorpholino, tetrahydropyranyl, 1,3-dioxolanyl, homopiperazinyl, thienyl,
 isoxazolyl, imidazolyl, pyrrolyl, thiazolyl, thiadiazolyl, isothiazolyl, 1,2,4-triazolyl, 1,2,3-
 triazolyl, pyranal, indolyl, pyrimidyl, pyrazinyl, pyridazinyl, pyridyl, 4-pyridonyl, quinolyl,
 tetrahydrothienyl 1,1-dioxide, 2-oxo-pyrrolidinyl and 1-isoquinolonyl. Preferred examples of
 10 "heterocyclyl" when referring to a 5/6 and 6/6 bicyclic ring system include benzofuranyl,
 benzimidazolyl, benzthiophenyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl,
 benzisoxazolyl, pyridoimidazolyl, pyrimidoimidazolyl, quinolynyl, isoquinolynyl,
 quinoxalynyl, quinazolinyl, phthalazinyl, cinnolynyl, imidazo[2,1-*b*][1,3]thiazolyl, chromanyl
 and naphthyridinyl. Preferably the term "heterocyclyl" refers to 5- or 6-membered
 15 monocyclic heterocyclic rings, such as oxazolyl, isoxazolyl, pyrrolidinyl, 2-pyrrolidinyl,
 2,5-dioxopyrrolidinyl, morpholino, furanyl, tetrahydrofuranyl, piperidyl, piperazinyl,
 thiomorpholino, tetrahydropyranyl, homopiperazinyl, thienyl, imidazolyl, 1,2,4-triazolyl,
 1,3,4-triazolyl, indolyl, thiazolyl, thiadiazolyl, pyrazinyl, pyridazinyl and pyridyl.

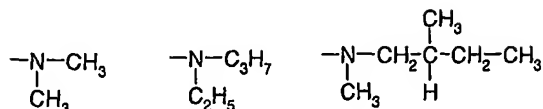
The term "cycloalkyl" refers to a saturated carbocyclic ring containing between 3 to 12
 20 carbon atoms, preferably between 3 and 7 carbon atoms. Examples of C₃₋₇cycloalkyl include
 cycloheptyl, cyclohexyl, cyclopentyl, cyclobutyl or cyclopropyl. Preferably cyclopropyl,
 cyclopentyl or cyclohexyl.

Examples of C₁₋₆alkyl include methyl, ethyl, propyl, isopropyl, 1-methyl-propyl, *sec*-
 butyl, *tert*-butyl and 2-ethyl-butyl; examples of C₂₋₆alkenyl include: ethenyl, 2-propenyl,
 25 2-butenyl, or 2-methyl-2-butenyl; examples of C₂₋₆alkynyl include: ethynyl, 2-propynyl,
 2-butyne, or 2-methyl-2-butyne, examples of -OC₁₋₆alkyl include methoxy, ethoxy, propoxy
 and *tert*-butoxy; examples of -C(O)OC₁₋₆alkyl include methoxycarbonyl, ethoxycarbonyl and
tert-butyloxycarbonyl; examples of -NH-C₁₋₄alkyl include:



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examples of -N-di-(C₁₋₄alkyl):



For the avoidance of doubt, in the definition of linker group 'X', the right hand side of the group is attached to phenyl ring and the left hand side is bound to 'Y'.

- 5 The invention includes the E and Z isomers of compounds of the invention defined above, but the preferred compounds are the E isomers. It is to be understood that, insofar as certain of the compounds of the invention may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the property of stimulating GLK
- 10 directly or inhibiting the GLK/GLKRP interaction. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form.

Preferred compounds of Formula (I) to (Ic) above or of Formula (II) to (IIf) below are

15 those wherein any one or more of the following apply:

- (1) **m** is 0 or 1;
 n is 1 or 2; preferably **n** is 2;
 most preferably **m** is 0 and **n** is 2.
- (2) The **R**¹ and/or **R**² group(s) are attached at the 2-position and/or the 3-position and/or
 the 5- position; when **n** + **m** is 2, the groups are preferably at the 2- and 5- or 3- and 5-
 positions, most preferably at the 2- and 5- positions.
- (3) each **R**¹ is independently selected from OH, CH_{3-a}F_a (preferably CF₃), OCH_{3-a}F_a
 (preferably OCF₃), halo, C₁₋₆alkyl (preferably methyl), NO₂ or heterocyclyl optionally
 substituted by C₁₋₆alkyl; preferably **R**¹ is selected from CH_{3-a}F_a (preferably CF₃),
 OCH_{3-a}F_a (preferably OCF₃) or halo;
 25 (4) each **R**² is the group Y-X-
 wherein each **X** is independently selected from:
 -O-Z-, -C(O)O-Z-, -S-Z-, -SO₂-Z-, -N(R⁶)SO₂-Z-, -SO₂NH-Z-, -(CH₂)₁₋₄-, -
 CH=CH-Z-, -C≡C-Z-, -N(R⁶)CO-Z-, -CON(R⁶)-Z- or a direct bond;
 30 Preferably **X** is independently selected from: -O-Z-, -S-Z-, -SO₂-Z-,
 -N(R⁶)SO₂-Z-, -SO₂NH-Z-, -(CH₂)₁₋₄- or a direct bond

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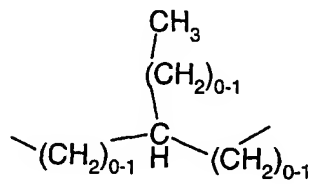
Most preferably **X** is independently selected from: -O-, -S-, -SO-, -SO₂-, -(CH₂)₁₋₄- or a direct bond;

each **Z** is independently selected from:

a direct bond or -(CH₂)₁₋₂, or a group of the formula -(CH₂)_p-C(R⁶)₂-(CH₂)_q-,

5 wherein one R⁶ group is hydrogen and the other R⁶ group is C₁₋₄alkyl;

preferably a direct bond, -(CH₂)₀₋₂- or



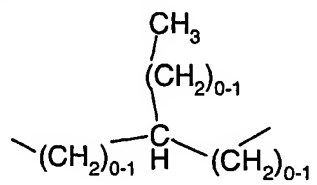
more preferably a direct bond or -CH₂-.

each **Z**¹ is independently selected from:

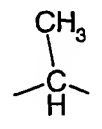
10 a direct bond, C₂₋₆alkenylene or a group of the formula -(CH₂)_p-C(R⁶)₂-(CH₂)_q-,

wherein one R⁶ group is hydrogen and the other R⁶ group is C₁₋₄alkyl;

preferably a direct bond, -(CH₂)₀₋₂-, C₂₋₄alkenylene or



more preferably a direct bond, -(CH₂)₀₋₄-, 2-propenylene or



15

most preferably -(CH₂)₀₋₃-, 2-propenylene or a direct bond.

and each **Y** is independently selected from:

aryl-Z¹-, heterocyclyl-Z¹-, C₃₋₇ cycloalkyl-Z¹-, C₁₋₆ alkyl, C₁₋₆alkoxy, C₂₋₆alkenyl or -CH(OH)CH_{3-a}F_a;

20 preferably each **Y** is independently selected from:

phenyl-Z¹-, heterocyclyl-Z¹-, C₃₋₇ cycloalkyl-Z¹-, C₁₋₆ alkyl (preferably a

branched C₂₋₆alkyl chain such as isopropyl or isobutyl), C₂₋₆alkenyl or -CH_{3-a}F_a;

most preferably **Y** is independently selected from:

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phenyl- Z^1 -, morpholinyl- Z^1 -, pyridyl- Z^1 -, pyrrolidino- Z^1 -, isoxazolyl- Z^1 -,
 diazolyl- Z^1 -, furanyl- Z^1 -, thienyl- Z^1 -, thiazolyl- Z^1 -, cyclopropyl- Z^1 - or
 cyclohexyl- Z^1 -,

wherein each Y is independently optionally substituted by R^4 .

- 5 (5) each R^2 is the group Y-X-, Z within the definition of X is a direct bond and Z^1 within the definition of Y is a group of the formula $-(CH_2)_p-C(R^6)_2-(CH_2)_q$ -.

most preferably R^2 is independently selected from: methoxy, methylthio, methylsulphinyl,
 methylsulphonyl, ethoxy, iso-propoxy, pentyloxy, phenoxy, benzyloxy,
 phenylpropoxy, phenylallyloxy, phenylthio, diazolylmethoxy, diazolylethoxy,
 10 furanylmethoxy, isoxazolylmethoxy, morpholino, pyridylmethoxy, pyrrolidinylethoxy,
 thiazolyl, thiazolylmethoxy, thiazolylethoxy, thienylmethoxy, cyclopropylmethoxy or
 cyclohexylmethoxy, wherein each of these R^2 groups is optionally substituted by R^4 .

- (6) each R^4 is independently selected from:

- halo, $-CH_3-aF_a$, $-OCH_3-aF_a$, CN, NO_2 , C_{1-6} alkyl, C_{1-6} alkoxy, $-COOH$,
 15 $-(CH_2)_{1-3}COOH$, $-(CH_2)_{0-3}COOH$, $-C(O)phenyl$, $-C(O)NH_2$, $-C(O)NH-phenyl$,
 $-SO_2NH_2$, $-SO_2C_{1-6}alkyl$, phenyl optionally substituted by $C_{1-6}alkyl$ or
 $-C(O)OC_{1-6}alkyl$;

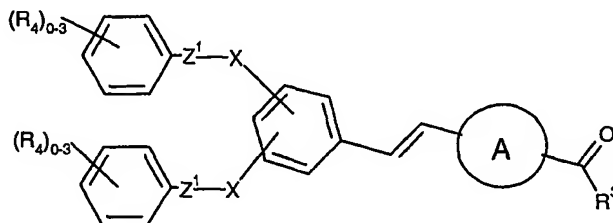
- More preferably R^4 is independently selected from. chloro, bromo, fluoro, methyl,
tert-butyl, isopropyl, methoxy, C_{1-4} alkoxycarbonyl, vinyl, CN, OH, trifluoromethyl,
 20 $-COOH$, $-CH_2COOH$, NO_2 , methylsulphonyl, $-C(O)NH_2$, $-C(O)NH-phenyl$,
 $-SO_2NH_2$ or benzyloxy,

- (7) R^3 is selected from hydrogen or C_{1-6} alkyl; preferably R^3 is selected from hydrogen
 or methyl; most preferably R^3 is hydrogen.

According to a further feature of the invention there is provided the following

- 25 preferred groups of compounds of the invention:

(I) a compound of Formula (II)



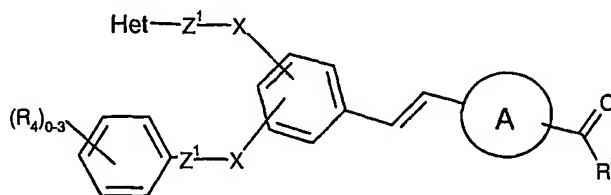
Formula (II)

- 14 -

wherein:

A, X, Z¹, R³ and R⁴ are as defined above in a compound of Formula (I);
or a salt, solvate or pro-drug thereof.

(II) a compound of Formula (IIa)



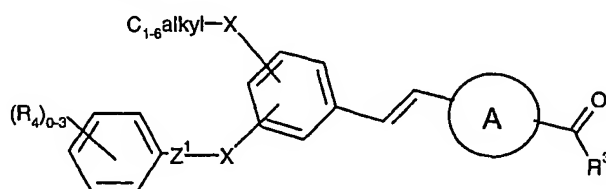
Formula (IIa)

wherein:

Het is a monocyclic heterocyclyl, optionally substituted with between 1 and 3 groups selected from R⁴ and,

A, X, Z¹, R³ and R⁴ are as defined above in a compound of Formula (I);
or a salt, solvate or pro-drug thereof.

(III) a compound of Formula (IIb)



Formula (IIb)

wherein:

the C₁₋₆alkyl group is optionally substituted with between 1 and 3 groups selected from R⁴, preferably unsubstituted;

the C₁₋₆alkyl group optionally contains a double bond, preferably the C₁₋₆alkyl group does not contain a double bond; and

A, X, Z¹, R³ and R⁴ are as defined above in a compound of Formula (I);

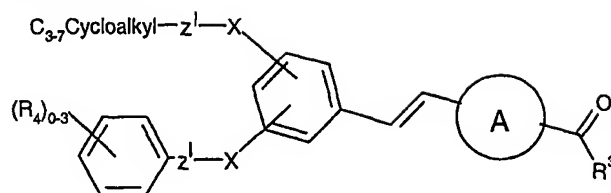
with the proviso that:

when A is pyridyl, R³ is OH, **phenyl-Z¹-X-** is phenyl-CH₂-O- wherein the phenyl ring is unsubstituted, then **C₁₋₆alkyl-X-** must be other than CH₃-S- or CH₃-SO₂-;

or a salt, solvate or pro-drug thereof.

- 15 -

(IV) a compound of Formula (IIc)

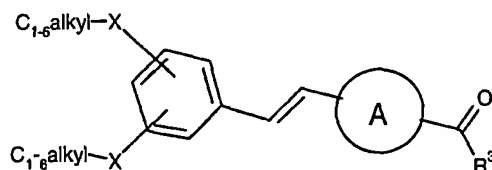


Formula (IIc)

wherein:

- 5 the C_{3-7} cycloalkyl group is optionally substituted with between 1 and 3 groups selected from R^4 , and
 A, X, Z^1 , R^3 and R^4 are as defined above in a compound of Formula (I);
 or a salt, solvate or pro-drug thereof.

(V) a compound of Formula (IId)

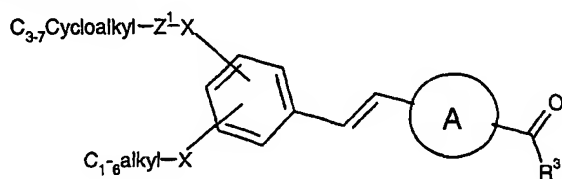


Formula (IId)

wherein:

- the C_{1-6} alkyl groups are independently optionally substituted with between 1 and 3 groups selected from R^4 , preferably one of the C_{1-6} alkyl groups is unsubstituted,
 15 the C_{1-6} alkyl groups independently optionally contain a double bond, preferably only one of the C_{1-6} alkyl groups contain a double bond, preferably neither of the C_{1-6} alkyl group contains a double bond, and
 A, X, R^3 and R^4 are as defined above in a compound of Formula (I);
 with the proviso that A is other than pyridyl, furanyl or thiazolyl;
 20 or a salt, solvate or pro-drug thereof.

(VI) a compound of Formula (IIe)



Formula (IIe)

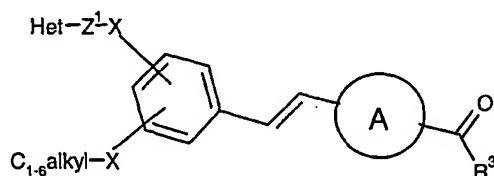
wherein:

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the C₃₋₇cycloalkyl and C₁₋₆alkyl groups are independently optionally substituted with between 1 and 3 groups selected from R⁴, preferably the C₁₋₆alkyl group is unsubstituted; the C₁₋₆alkyl group optionally contains a double bond, preferably the C₁₋₆alkyl group does not contains a double bond; and

- 5 A, X, Z¹, R³ and R⁴ are as defined above in a compound of Formula (I);
or a salt, solvate or pro-drug thereof.

(VII) a compound of Formula (IIf)



Formula (IIf)

- 10 wherein:

Het is a monocyclic heterocyclyl,

the Het and C₁₋₆alkyl groups are independently optionally substituted with between

1 and 3 groups selected from R⁴, preferably the C₁₋₆alkyl group is unsubstituted;

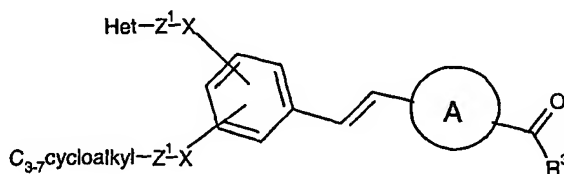
the C₁₋₆alkyl group optionally contains a double bond, preferably the C₁₋₆alkyl group does

- 15 not contains a double bond; and

A, X, Z¹, R³ and R⁴ are as defined above in a compound of Formula (I);

or a salt, solvate or pro-drug thereof.

(VIII) a compound of Formula (IIg)



Formula (IIg)

- 20

wherein:

Het is a monocyclic heterocyclyl,

the Het and C₃₋₇cycloalkyl groups are independently optionally substituted with between

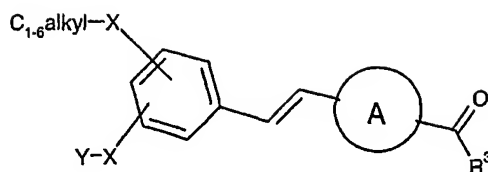
1 and 3 groups selected from R⁴, and

- 25 A, X, Z¹, R³ and R⁴ are as defined above in a compound of Formula (I);

or a salt, solvate or pro-drug thereof.

(IX) a compound of Formula (IIh)

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Formula (IIh)

wherein:

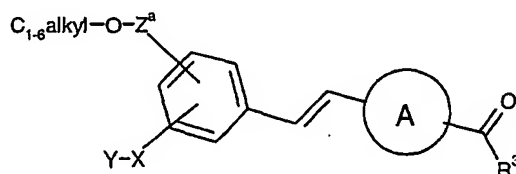
Y is aryl-Z¹-, wherein aryl is preferably a partially saturated bicyclic carbocyclic ring;

- 5 Y and the C₁₋₆alkyl group are independently optionally substituted with between 1 and 3 groups selected from R⁴, preferably the C₁₋₆alkyl group is unsubstituted, the C₁₋₆alkyl group optionally contains a double bond, preferably the C₁₋₆alkyl group does not contains a double bond; and

A, X, Z¹, R³ and R⁴ are as defined above in a compound of Formula (I);

- 10 or a salt, solvate or pro-drug thereof.

(X) a compound of Formula (IIj)



Formula (IIj)

wherein:

- 15 X is selected from -SO₂N(R⁶)-Z- or -N(R⁶)SO₂-Z-, preferably X is -SO₂N(R⁶)-Z-;

Z is as described above, preferably Z is propylene, ethylene or methylene, more preferably Z is methylene;

Z^a is selected from a direct bond or a group of the formula -(CH₂)_p-C(R⁶)₂-(CH₂)_q-;

- 20 preferably Z^a is selected from C₁₋₂alkylene or a direct bond; preferably Z^a is a direct bond;

R⁶ is selected from: C₁₋₄alkyl or hydrogen, preferably methyl or hydrogen;

Y is selected from aryl-Z¹- or heterocyclyl-Z¹-;

Y and the C₁₋₆alkyl group are independently optionally substituted with between 1 and 3 groups selected from R⁴,

- 25 the C₁₋₆alkyl group optionally contains a double bond, preferably the C₁₋₆alkyl group does not contain a double bond, and

A, Z¹, R³ and R⁴ are as defined above in a compound of Formula (I);

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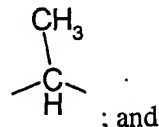
or a salt, solvate or pro-drug thereof.

A further preferred groups of compounds of the invention in either of groups (I)-(IX) above is wherein:

X is independently selected from: -O-Z-, SO₂N(R⁶)-Z- or -N(R⁶)-Z-;

5 Z is a direct bond or -CH₂-;

Z¹ is selected from a direct bond, -CH₂- -(CH₂)₂- or



R³ is as defined above in a compound of Formula (I);

or a salt, solvate or pro-drug thereof.

10 In a further embodiment of the invention there is provided a compound as defined in either of groups (I) to (X) above wherein:

A is selected from: pyridyl, pyrimidinyl, pyrazinyl, furanyl or thiazolyl; preferably A is linked to the styryl group at the 2-position of A.

In a further embodiment of the invention there is provided a compound as defined in
15 either of groups (I) to (X) above wherein the two Y-X- groups are linked to the phenyl ring in a 2, 5 orientation relative to the styryl group.

The compounds of the invention may be administered in the form of a pro-drug. A pro-drug is a bioprecursor or pharmaceutically acceptable compound being degradable in the body to produce a compound of the invention (such as an ester or amide of a
20 compound of the invention, particularly an *in vivo* hydrolysable ester). Various forms of prodrugs are known in the art. For examples of such prodrug derivatives, see:

- a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);
- b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen;
- 25 c) H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);
- d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
- e) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and
- f) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

30 The contents of the above cited documents are incorporated herein by reference.

Examples of pro-drugs are as follows. An in-vivo hydrolysable ester of a compound of the invention containing a carboxy or a hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically-acceptable esters for carboxy include

5 C₁ to C₆alkoxymethyl esters for example methoxymethyl, C₁ to ₆alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C₃ to ₈cycloalkoxycarbonyloxyC₁ to ₆alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters, for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C₁-₆alkoxycarbonyloxyethyl esters.

An in-vivo hydrolysable ester of a compound of the invention containing a hydroxy
10 group includes inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α -acyloxyalkyl ethers and related compounds which as a result of the in-vivo hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α -acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of in-vivo hydrolysable ester forming groups for hydroxy include alkanoyl,
15 benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

A suitable pharmaceutically-acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for
20 example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically-acceptable salt of a benzoxazinone derivative of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an
25 ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

A further feature of the invention is a pharmaceutical composition comprising a
30 compound of Formula (I) to (Ic) or (II) to (IIj) as defined above, or a salt, solvate or prodrug thereof, together with a pharmaceutically-acceptable diluent or carrier.

- 20 -

According to another aspect of the invention there is provided a compound of Formula (Ib) or (Ic), or (II) to (IIj) as defined above for use as a medicament;

with the proviso that

- (i) when A is pyridyl or thiazolyl, m is 1 or 2 and n is 0, R³ is OH or -O-C₁₋₆alkyl, then R¹ is
5 other than halo, amino or nitro;
- (ii) when A is pyridyl, m = 0, n = 1, X is -N(CH₃)- or -N(CH₃)-CH₂-, R³ is OH, then Y cannot be methyl;
- (iii) when A is thiazolyl, m is 0, R³ is OH, then when n is 2 (R²)_n cannot be di-C₁₋₆alkyl-O- or C₁₋₆alkyl-O- C₁₋₆alkenyl-O- and when n is 3 (R²)_n cannot be tri-C₁₋₆alkyl-O-;
- 10 (iv) when A is pyridyl, m is 0 or m is 1 and R¹ is halo, n is 1 and R² is phenyl-CH₂-O-, then R³ cannot be OH; and
- (v) when A is pyridyl, R³ is OH, m is 0, n is 2 and one of the R² groups is phenyl-CH₂-O-, then the other R² group must be other than CH₃-S- or CH₃-SO₂-.

Further according to the invention there is provided a compound of Formula (Ib) or
15 (Ic), or (II) to (IIj) for use in the preparation of a medicament for treatment of a disease mediated through GLK, in particular type 2 diabetes.

The compound is suitably formulated as a pharmaceutical composition for use in this way.

20 According to another aspect of the present invention there is provided a method of treating GLK mediated diseases, especially diabetes, by administering an effective amount of a compound of Formula (Ib) or (Ic), or (II) to (IIj) to a mammal in need of such treatment.

Specific disease which may be treated by the compound or composition of the
25 invention include: blood glucose lowering in Diabetes Mellitus type 2 without a serious risk of hypoglycaemia (and potential to treat type 1), dyslipidemia, obesity, insulin resistance, metabolic syndrome X, impaired glucose tolerance.

Specific disease which may be treated by the compound or composition of the
30 invention include: blood glucose lowering in Diabetes Mellitus type 2 (and potential to treat type 1); dyslipidaemia; obesity; insulin resistance; metabolic syndrome X; impaired glucose tolerance; polycystic ovary syndrome.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for
5 example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures
10 using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium
15 carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the
20 gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with
25 water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation
30 products of an alkylene oxide with fatty acids (for example polyoxyethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or

condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and
5 hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable
10 oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

15 Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

20 The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial
25 esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol,
30 propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using

one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

5 Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

10 For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

 The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the
15 particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information
20 on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

 The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula (I), (Ia), (Ib) or (Ic) will naturally vary according to the nature and severity of the
25 conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

 In using a compound of the Formula (I), (Ia), (Ib) or (Ic) for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses.
30 In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose

in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred.

The elevation of GLK activity described herein may be applied as a sole therapy or may involve, in addition to the subject of the present invention, one or more other substances
5 and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. Simultaneous treatment may be in a single tablet or in separate tablets. For example in the treatment of diabetes mellitus chemotherapy may include the following main categories of treatment:

- 10 1) Insulin and insulin analogues;
- 2) Insulin secretagogues including sulphonylureas (for example glibenclamide, glipizide) and prandial glucose regulators (for example repaglinide, nateglinide);
- 3) Insulin sensitising agents including PPAR γ agonists (for example pioglitazone and rosiglitazone);
- 15 4) Agents that suppress hepatic glucose output (for example metformin).
- 5) Agents designed to reduce the absorption of glucose from the intestine (for example acarbose);
- 6) Agents designed to treat the complications of prolonged hyperglycaemia;
- 7) Anti-obesity agents (for example sibutramine and orlistat);
- 20 8) Anti- dyslipidaemia agents such as, HMG-CoA reductase inhibitors (statins, eg pravastatin); PPAR α agonists (fibrates, eg gemfibrozil); bile acid sequestrants (cholestyramine); cholesterol absorption inhibitors (plant stanols, synthetic inhibitors); bile acid absorption inhibitors (IBATi) and nicotinic acid and analogues (niacin and slow release formulations);
- 25 9) Antihypertensive agents such as, β blockers (eg atenolol, inderal); ACE inhibitors (eg lisinopril); Calcium antagonists (eg. nifedipine); Angiotensin receptor antagonists (eg candesartan), α antagonists and diuretic agents (eg. furosemide, benzthiazide);
- 10) Haemostasis modulators such as, antithrombotics, activators of fibrinolysis and antiplatelet agents; thrombin antagonists; factor Xa inhibitors; factor VIIa inhibitors);
- 30 antiplatelet agents (eg. aspirin, clopidogrel); anticoagulants (heparin and Low molecular weight analogues, hirudin) and warfarin; and

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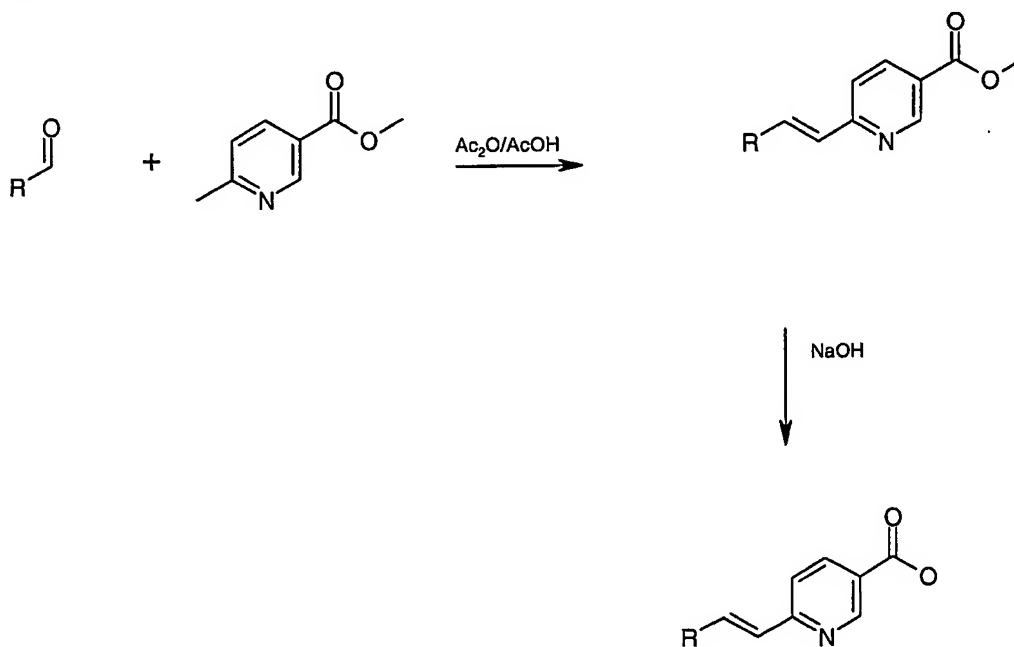
- 11) Anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs (eg. aspirin) and steroidal anti-inflammatory agents (eg. cortisone).

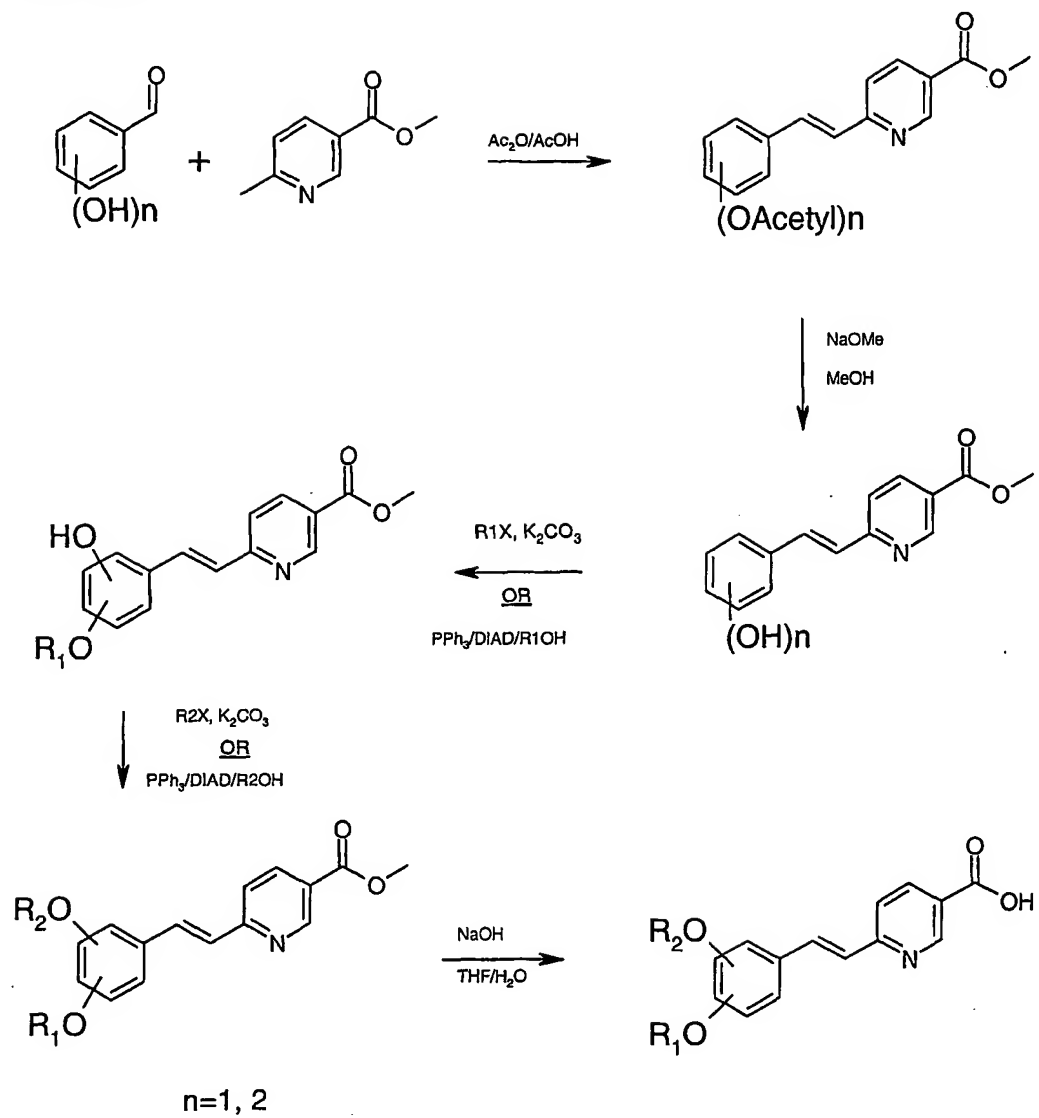
According to another aspect of the present invention there is provided individual compounds produced as end products in the Examples set out below and salts thereof.

- 5 A compound of the invention, or a salt, pro-drug or solvate thereof, may be prepared by any process known to be applicable to the preparation of such compounds or structurally related compounds. Such processes are illustrated by the following representative schemes (1 to 4) in which variable groups have any of the meanings defined for Formula (I) unless stated otherwise and A is for example depicted as pyridyl. Functional groups may be protected and
10 deprotected using conventional methods.

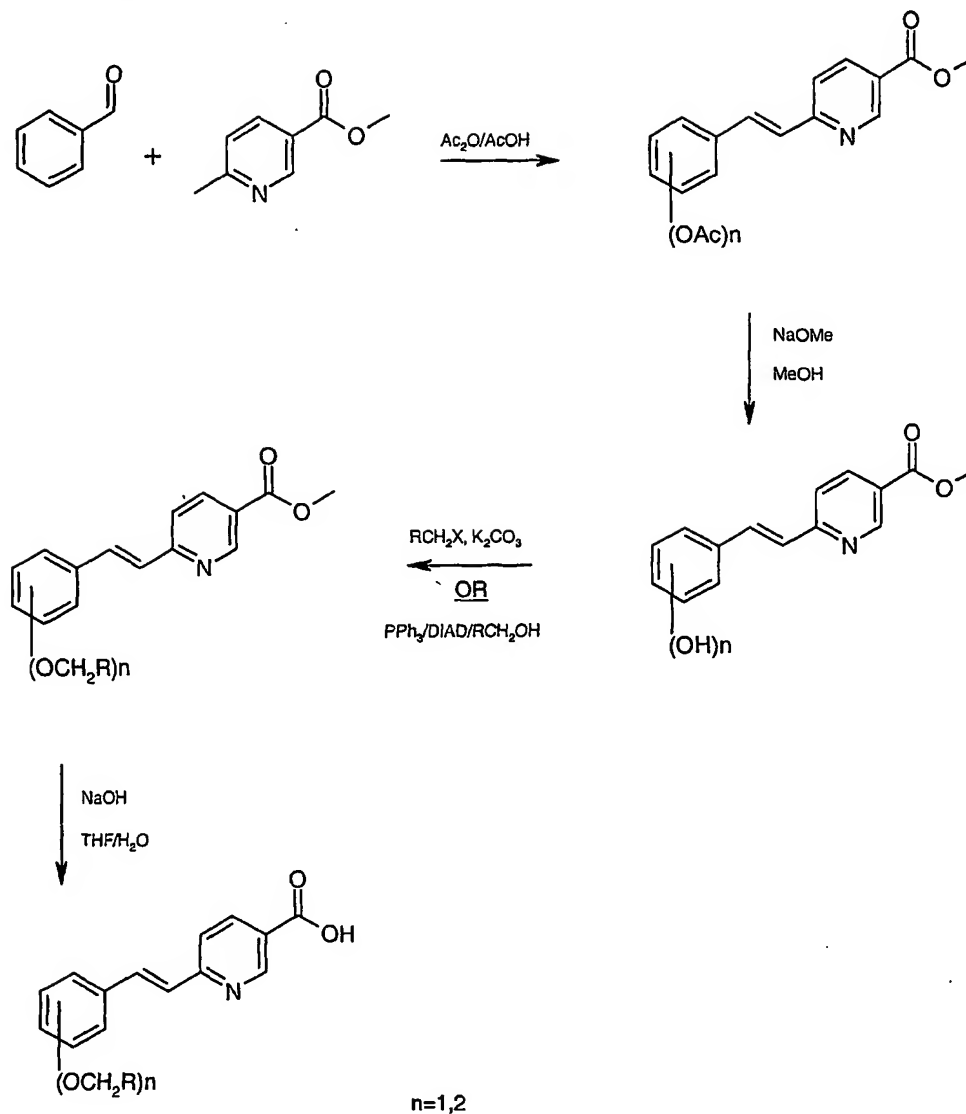
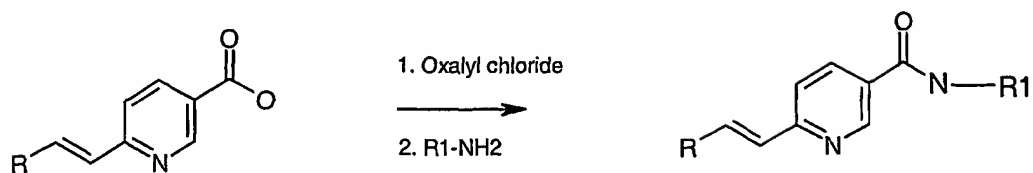
For examples of protecting groups such as amino and carboxylic acid protecting groups (as well as means of formation and eventual deprotection), see T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", Second Edition, John Wiley & Sons, New York, 1991. Note abbreviations used have been listed immediately before the Examples
15 below.

SCHEME 1



SCHEME 2

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SCHEME 3**SCHEME 4**

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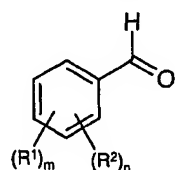
During the preparation process, it may be advantageous to use a protecting group for a functional group within the molecule. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect

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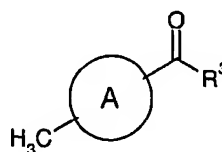
removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Processes for the synthesis of compounds of Formula (I) are provided as a further feature of the invention. Thus, according to a further aspect of the invention there is provided a process for the preparation of a compound of Formula (I) which comprises:

(a) reaction of a compound of Formula (IIIa) with a compound of Formula (IIIb),

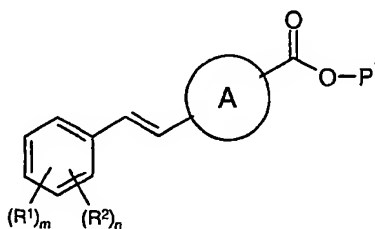


Formula (IIIa)



Formula (IIIb);

(b) for compounds of Formula (I) wherein R³ is hydrogen, de-protection of a compound of Formula (IIIc),



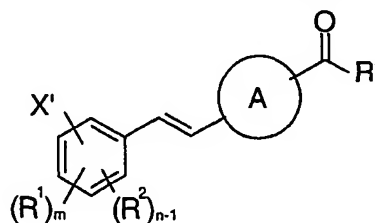
Formula (IIIc)

wherein P¹ is a protecting group;

(c) reaction of a compound of Formula (IIId) with a compound of Formula (IIIe),



Formula (IIId)



Formula (IIIe)

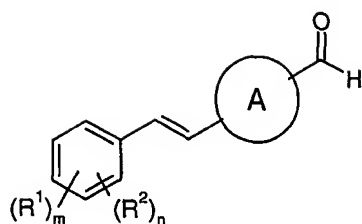
wherein X' and X'' comprises groups which when reacted together form the group X;

(d) for a compound of Formula (I) wherein X or X¹ is -SO-Z- or -SO₂-Z-, oxidation of the

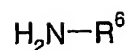
corresponding compound of Formula (I) wherein X or X¹ respectively is -S-Z-; or

(e) for a compound of Formula (I) wherein R³ is NHR⁶, reaction of a compound of Formula (IIIf) with a compound of Formula (IIIg),

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Formula (IIIg)



Formula (IIIg);

and thereafter, if necessary:

- i) converting a compound of Formula (I) into another compound of Formula (I);
- 5 ii) removing any protecting groups;
- iii) forming a salt, pro-drug or solvate thereof.

Specific reaction conditions for the above reactions are as follows:

Process a) – as described above in Scheme 1;

Process b) – as described above in Scheme 1/2

10 *Process c)* – examples of this process are as follows:

- (i) to form a group when X is –O-Z-, X' is a group of formula HO-Z- and X'' is a leaving group (alternatively X' is a group of formula L²-Z- wherein L² is a leaving group and X'' is a hydroxyl group), compounds of Formula (IIIc) and (IIIe) are reacted together in a suitable solvent, such as DMF or THF, with a base such as sodium hydride or potassium *tert*-butoxide, at a temperature in the range 0 to 100°C, optionally using metal catalysis such as palladium on carbon or cuprous iodide;
- 15 (ii) to form a group when X is N(R⁶)-Z-, X' is a group of formula H-(R⁶)N-Z- and X'' is a leaving group (alternatively X' is a group of formula L²-Z- wherein L² is a leaving group and X'' is a group or formula –N(R⁶)-H), compounds of Formula (IIIc) and (IIIe) are reacted together in a suitable solvent such as THF, an alcohol or acetonitrile, using a reducing agent such as sodium cyano borohydride or sodium trisacetoxymethylborohydride at room temperature;
- 20 (iii) to form a group when X is –SO₂N(R⁶)-Z-, X' is a group of formula H-N(R⁶)-Z- wherein L² is a leaving group and X'' is an activated sulphonyl group such as a group of formula –SO₂-Cl, compounds of Formula (IIIc) and (IIIe) are reacted together in a suitable solvent such as methylene chloride, THF or pyridine, in the presence of a base such as triethylamine or pyridine at room temperature;
- 25 (iv) to form a group when X is –N(R⁶)SO₂-Z-, X' is an activated sulphonyl group such as a group of formula Cl-SO₂-Z- group and X'' is a group of formula –N(R⁶)-L² wherein L² is

- 30 -

a leaving group, compounds of Formula (III_d) and (III_e) are reacted together in a suitable solvent such as methylene chloride, THF or pyridine, in the presence of a base such as triethylamine or pyridine at room temperature;

- 5 (v) to form a group when X is $-C(O)N(R^6)-Z-$, X' is a group of formula $H-N(R^6)-Z-$ wherein L^2 is a leaving group and X'' is an activated carbonyl group such as a group of formula $-C(O)-Cl$, compounds of Formula (III_d) and (III_e) are reacted together in a suitable solvent such as THF or methylene chloride, in the presence of a base such as triethylamine or pyridine at room temperature;
- 10 (vi) to form a group when X is $-N(R^6)C(O)-Z-$, X' is an activated carbonyl group such as a group of formula $Cl-C(O)-Z-$ group and X'' is a group of formula $-N(R^6)-L^2$ wherein L^2 is a leaving group, compounds of Formula (III_d) and (III_e) are reacted together in a suitable solvent such as THF or methylene chloride, in the presence of a base such as triethylamine or pyridine at room temperature;
- 15 (vii) to form a group when X is $-CH=CH-Z-$, a Wittig reaction or a Wadsworth-Emmans Horner reaction can be used. For example, X' terminates in an aldehyde group and Y-X'' is a phosphine derivative of the formula $Y-C^H-P^+PH_3$ which can be reacted together in a strong base such as sodium hydride or potassium *tert*-butoxide, in a suitable solvent such as THF at a temperature between room temperature and 100°C.

Process d) - the oxidization of a compound of Formula (I) wherein X or X¹ is $-S-Z-$ is well known in the art, for example, reaction with metachloroperbenzoic acid (MCPBA) is the presence of a suitable solvent such as dichloromethane at ambient temperature. If an excess of MCPBA is used a compound of Formula (I) wherein X is $-S(O_2)-$ is obtained.

Process e) - as described above in Scheme 4.

Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower" signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use

of protecting groups and methods of deprotection not specifically mentioned is of course within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or araliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 5 1-20 carbon atoms). Examples of carboxy protecting groups include straight or branched chain (C₁₋₁₂)alkyl groups (e.g. isopropyl, *t*-butyl); lower alkoxy lower alkyl groups (e.g. methoxymethyl, ethoxymethyl, isobutoxymethyl; lower aliphatic acyloxy lower alkyl groups, (e.g. acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl); lower alkoxycarbonyloxy lower alkyl groups (e.g. 1-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl); aryl lower alkyl 10 groups (e.g. *p*-methoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (e.g. trimethylsilyl and *t*-butyldimethylsilyl); tri(lower alkyl)silyl lower alkyl groups (e.g. trimethylsilylethyl); and (2-6C)alkenyl groups (e.g. allyl and vinyl ethyl).

Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, metal- or enzymically-catalysed hydrolysis.

15 Examples of hydroxy protecting groups include lower alkenyl groups (e.g. allyl); lower alkanoyl groups (e.g. acetyl); lower alkoxycarbonyl groups (e.g. *t*-butoxycarbonyl); lower alkenyloxycarbonyl groups (e.g. allyloxycarbonyl); aryl lower alkoxycarbonyl groups (e.g. benzyloxycarbonyl, *p*-methoxybenzyloxycarbonyl, *o*-nitrobenzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl); tri lower alkyl/arylsilyl groups (e.g. trimethylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl); aryl lower alkyl groups (e.g. benzyl) groups; and triaryl 20 lower alkyl groups (e.g. triphenylmethyl).

Examples of amino protecting groups include formyl, aralkyl groups (e.g. benzyl and substituted benzyl, e.g. *p*-methoxybenzyl, nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-*p*-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (e.g. 25 *t*-butoxycarbonyl); lower alkenyloxycarbonyl (e.g. allyloxycarbonyl); aryl lower alkoxycarbonyl groups (e.g. benzyloxycarbonyl, *p*-methoxybenzyloxycarbonyl, *o*-nitrobenzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl); trialkylsilyl (e.g. trimethylsilyl and *t*-butyldimethylsilyl); alkylidene (e.g. methyldiene); benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for 30 example, acid-, base, metal- or enzymically-catalysed hydrolysis, or photolytically for groups such as *o*-nitrobenzyloxycarbonyl, or with fluoride ions for silyl groups.

Examples of protecting groups for amide groups include aralkoxymethyl (e.g. benzyloxymethyl and substituted benzyloxymethyl); alkoxymethyl (e.g. methoxymethyl and

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trimethylsilylethoxymethyl); tri alkyl/arylsilyl (e.g. trimethylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl); tri alkyl/arylsilyloxymethyl (e.g. *t*-butyldimethylsilyloxymethyl, *t*-butyldiphenylsilyloxymethyl); 4-alkoxyphenyl (e.g. 4-methoxyphenyl); 2,4-di(alkoxy)phenyl (e.g. 2,4-dimethoxyphenyl); 4-alkoxybenzyl (e.g. 4-methoxybenzyl); 2,4-di(alkoxy)benzyl (e.g. 2,4-di(methoxy)benzyl); and alk-1-enyl (e.g. allyl, but-1-enyl and substituted vinyl e.g. 2-phenylvinyl).

Aralkoxymethyl groups may be introduced onto the amide group by reacting the latter group with the appropriate aralkoxymethyl chloride, and removed by catalytic hydrogenation. Alkoxymethyl, tri alkyl/arylsilyl and tri alkyl/silyloxymethyl groups may be introduced by reacting the amide with the appropriate chloride and removing with acid; or in the case of the silyl containing groups, fluoride ions. The alkoxyphenyl and alkoxybenzyl groups are conveniently introduced by arylation or alkylation with an appropriate halide and removed by oxidation with ceric ammonium nitrate. Finally alk-1-enyl groups may be introduced by reacting the amide with the appropriate aldehyde and removed with acid.

15

The present invention also relates to the use of a GLK activator for the combined treatment of diabetes and obesity. GLK and GLKRP and the K_{ATP} channel are expressed in neurones of the hypothalamus, a region of the brain that is important in the regulation of energy balance and the control of food intake [14-18]. These neurones have been shown to express orectic and anorectic neuropeptides [15, 19, 20] and have been assumed to be the glucose-sensing neurones within the hypothalamus that are either inhibited or excited by changes in ambient glucose concentrations [17, 19, 21, 22]. The ability of these neurones to sense changes in glucose levels is defective in a variety of genetic and experimentally induced models of obesity [23-28]. Intracerebroventricular (icv) infusion of glucose analogues, that are competitive inhibitors of glucokinase, stimulate food intake in lean rats [29, 30]. In contrast, icv infusion of glucose suppresses feeding [31]. Thus, small molecule activators of GLK may decrease food intake and weight gain through central effects on GLK. Therefore, GLK activators may be of therapeutic use in treating eating disorders, including obesity, in addition to diabetes. The hypothalamic effects will be additive or synergistic to the effects of the same compounds acting in the liver and/or pancreas in normalising glucose homeostasis, for the treatment of Type 2 diabetes. Thus the GLK/GLKRP system can be described as a potential "Diabesity" target (of benefit in both Diabetes and Obesity).

30

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This according to a second aspect of the invention there is provided the use of a GLK activator in the preparation of a medicament for the combined treatment or prevention of diabetes and obesity.

According to a further feature of the second aspect of the invention there is
5 provided a method of combined treatment, in a warm-blooded animal, of diabetes and obesity, comprising administering a therapeutically effective amount of a compound of a GLK activator, or a pharmaceutically-acceptable salt, pro-drug or solvate thereof.

According to a further feature of the second aspect of the invention there is
provided a pharmaceutical composition comprising a GLK activator, or a pharmaceutically
10 acceptable salt, prodrug or solvate thereof, in admixture with a pharmaceutically-acceptable diluent or carrier for the combined treatment of diabetes and obesity in a warm-blooded animal.

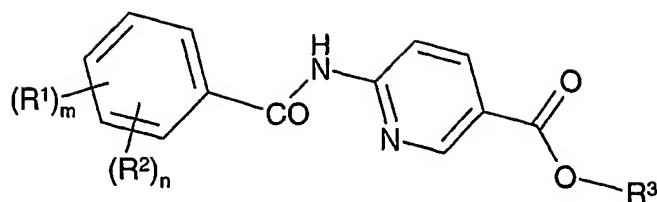
According to a further feature of the second aspect of the invention there is provided the
use a GLK activator in the preparation of a medicament for the treatment or prevention of
15 diabetes and obesity, wherein the GLK activator is a compound of Formula (I) above.

According to a further feature of the second aspect of the invention there is
provided a method of combined treatment, in a warm-blooded animal, of diabetes and
obesity, comprising administering a therapeutically effective amount of a compound of a
GLK activator, or a pharmaceutically-acceptable salt, pro-drug or solvate thereof, wherein
20 the GLK activator is a compound of Formula (I) above.

According to a further feature of the second aspect of the invention there is
provided a pharmaceutical composition comprising a GLK activator, or a pharmaceutically
acceptable salt, prodrug or solvate thereof, in admixture with a
pharmaceutically-acceptable diluent or carrier for the combined treatment of diabetes and
25 obesity in a warm-blooded animal, wherein the GLK activator is a compound of Formula
(I) above.

According to a further feature of the second aspect of the invention there is provided the
use a GLK activator in the preparation of a medicament for the treatment or prevention of
diabetes and obesity, wherein the GLK activator is a compound of Formula (IV) below.

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Formula (IV)

wherein

 m is 0, 1 or 2;5 n is 0, 1, 2, 3 or 4;and $n + m > 0$;

each R^1 is independently selected from OH, $-(CH_2)_{1-4}OH$, $-CH_3-aF_a$, $-(CH_2)_{1-4}CH_3-aF_a$, halo, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, NO_2 , NH_2 , $-NH-C_{1-4}alkyl$, $-N-di-(C_{1-4}alkyl)$, CN or formyl;

10 each R^2 is the group $Y-X-$ wherein each X is a linker independently selected from:

$-O-Z-$, $-O-Z-O-Z-$, $-C(O)O-Z-$, $-OC(O)-Z-$, $-S-Z-$, $-SO-Z-$, $-SO_2-Z-$, $-N(R^6)-Z-$, $-N(R^6)SO_2-Z-$, $-SO_2N(R^6)-Z-$, $-(CH_2)_{1-4}-$, $-CH=CH-Z-$, $-C\equiv C-Z-$, $-N(R^6)CO-Z-$, $-CON(R^6)-Z-$, $-C(O)N(R^6)S(O)_2-Z-$, $-S(O)_2N(R^6)C(O)-Z-$, $-C(O)-Z-$ or a direct

15 bond;

each Z is independently a direct bond or a group of the formula $-(CH_2)_p-C(R^6)_2-(CH_2)_q-$;each Y is independently selected from aryl- Z^1- , heterocyclyl- Z^1- , $C_{3-7}cycloalkyl-Z^1-$,

$C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$ or $-(CH_2)_{1-4}CH_3-aF_a$; wherein each Y is independently optionally substituted by up to 3 R^4 groups;

20 each R^4 is independently selected from halo, $-CH_3-aF_a$, CN, NO_2 , NH_2 , $C_{1-6}alkyl$, $-OC_{1-6}alkyl$, $-COOH$, $-C(O)OC_{1-6}alkyl$, OH or phenyl,or R^5-X^1- , where X^1 is independently as defined in X above and R^5 is

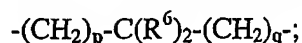
selected from hydrogen, $C_{1-6}alkyl$, $-CH_3-aF_a$, phenyl, naphthyl, heterocyclyl or $C_{3-7}cycloalkyl$; and R^5 is optionally substituted by halo, $C_{1-6}alkyl$,

25 $-CH_3-aF_a$, CN, NO_2 , NH_2 , $COOH$ or $-C(O)OC_{1-6}alkyl$,

wherein each phenyl, naphthyl or heterocyclyl ring in R^5 is optionally substituted by halo, CH_3-aF_a , CN, NO_2 , NH_2 , $C_{1-6}alkyl$, $-OC_{1-6}alkyl$, $COOH$, $-C(O)OC_{1-6}alkyl$ or OH;

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each Z^1 is independently a direct bond or a group of the formula



R^3 is selected from hydrogen or C_{1-6} alkyl; and

R^6 is independently selected from hydrogen, C_{1-6} alkyl or $-C_{2-4}$ alkyl-O- C_{1-4} alkyl;

5 each a is independently 1, 2 or 3;

p is an integer between 0 and 2;

q is an integer between 0 and 2;

and $p + q < 4$.

According to a further feature of the second aspect of the invention there is
10 provided a method of combined treatment, in a warm-blooded animal, of diabetes and obesity, comprising administering a therapeutically effective amount of a compound of a GLK activator, or a pharmaceutically-acceptable salt, pro-drug or solvate thereof, wherein the GLK activator is a compound of Formula (IV).

According to a further feature of the second aspect of the invention there is
15 provided a pharmaceutical composition comprising a GLK activator, or a pharmaceutically acceptable salt, prodrug or solvate thereof, in admixture with a pharmaceutically-acceptable diluent or carrier for the combined treatment of diabetes and obesity in a warm-blooded animal, wherein the GLK activator is a compound of Formula (IV).

20 Further examples of GLK activators are contained in International Application numbers: WO 00/58293, WO 01/44216, WO 01/83465, WO 01/83478, WO 01/85706, WO 01/85707, WO 02/08209 and WO 02/14312. The contents of aforesaid International Applications are hereby incorporated by reference.

In a further feature of the second aspect of the invention there is provided the use a GLK
25 activator in the preparation of a medicament for the treatment or prevention of diabetes and obesity, wherein the GLK activator is a compound exemplified in aforesaid International Applications or falls within the scope of aforesaid International Applications.

According to a further feature of the second aspect of the invention there is
provided a method of combined treatment, in a warm-blooded animal, of diabetes and
30 obesity, comprising administering a therapeutically effective amount of a compound of a GLK activator, wherein the GLK activator is a compound exemplified in aforesaid International Applications or falls within the scope of aforesaid International Applications.

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According to a further feature of the second aspect of the invention there is provided a pharmaceutical composition comprising a GLK activator, or a pharmaceutically acceptable salt, prodrug or solvate thereof, in admixture with a pharmaceutically-acceptable diluent or carrier for the combined treatment of diabetes and obesity in a warm-blooded animal, wherein the GLK activator is a compound exemplified in aforesaid International Applications or falls within the scope of aforesaid International Applications.

The identification of compounds that are useful in the combined treatment of diabetes and obesity is the subject of the present invention. These properties may be assessed, for example, by measuring changes in food intake, feeding-related behaviour (eg. feeding, grooming, physical activity, rest) and body weight separately or together with measuring plasma or blood glucose or insulin concentrations with or without an oral glucose load/food in a variety of animal models such as ob/ob mouse, db/db mouse, Fatty Zucker rat, Zucker diabetic rat (ZDF), streptozotocin-treated rats or mice or diet-induced obese mice or rats, as described in Sima & Shafrir, 2001, Animal Models of Diabetes, A Primer (Harwood Academic Publishers, Netherlands) or in animals treated with glucose directly into the brain or in animals rendered diabetic by treatment with streptozotocin and fed a high fat diet (Metabolism 49: 1390-4, 2000).

GLK activators may be used in the combined treatment of diabetes and obesity alone or in combination with one or more additional therapies. Such combination therapy may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. Simultaneous treatment may be in a single tablet or in separate tablets. Examples of agents which may be used in combination therapy include those listed in paragraphs 1) -11) above, as drugs which may be used with compounds of Formula (I).

The following examples of Compounds of Formula (I) – (Ic) are for illustration purposes and are not intended to limit the scope of this application. Each exemplified compound represents a particular and independent aspect of the invention. In the following non-limiting Examples, unless otherwise stated:

(i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

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(ii) operations were carried out at room temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon or nitrogen;

(iii) yields are given for illustration only and are not necessarily the maximum attainable;

5 (iv) the structures of the end-products of the Formula (I) were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin, quintet;

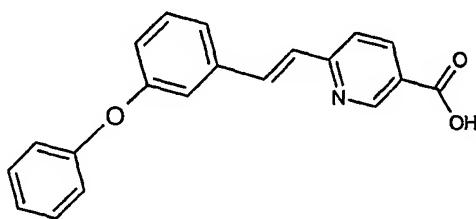
10 (v) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis;

(vi) chromatography was performed on silica (Merck Silica gel 60, 0.040 - 0.063 mm, 230 - 400 mesh); and

15 (vi) Biotage cartridges refer to pre-packed silica cartridges (from 40g up to 400g), eluted using a biotage pump and fraction collector system; Biotage UK Ltd, Hertford, Herts, UK.

EXAMPLE A

20 Scheme 1: Preparation of 6-(E-3-phenoxy-phenyl)-vinyl)-nicotinic acid



To a mixture of 6-methylnicotinate (151 mg, 1 mmol), acetic anhydride (541 mg, 5.3 mmol) and acetic acid (52 mg, 0.87 mmol) was added 3-(hydroxybenzyl)benzaldehyde (201 mg, 1.01 mmol). The reaction was heated to 120°C for 24 hours and was then cooled to room
25 temperature before ethyl acetate (5 ml) and water (5 ml) were added. The biphasic mixture was separated and the organic phase was washed with an aqueous saturated solution of sodium bicarbonate (5 ml). The organic phase was then filtered through magnesium sulfate absorbed onto silica gel and was concentrated *in vacuo*. The crude product was

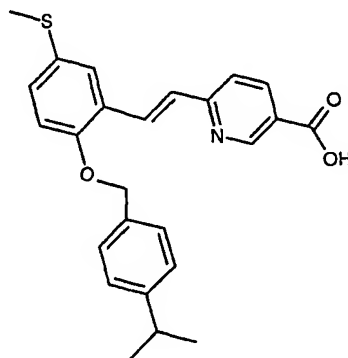
- 38 -

chromatographed on Kieselgel 60, eluting with a gradient of 10-40% ethyl acetate in *iso*-hexane to give the product as a white solid (162 mg, 49% yield); MS $[M+H]^+$ 332.

The product from the previous step (162 mg) was dissolved in a mixture of THF (2.5 ml) and 5 1M aqueous NaOH solution (1.25 ml) and was then heated for 2 hours at 60°C. The reaction was allowed to cool to room temperature overnight and was then reduced *in vacuo* to remove the THF. 1N aqueous HCl was added to precipitate out 6-(E-3-phenoxy-phenyl)-vinyl)-nicotinic acid which was isolated by filtration as a white solid (117 mg, 76% yield); 1H NMR δ (d_6 -DMSO) 6.95-7.85 (12H, m), 8.25 (1H, dd), 9.05 (1H, d), 13.30 (1H, br, s); MS $[M+H]^+$ 318.

EXAMPLE B

Scheme 2: Preparation of 6-(E-2-[2-(4-isopropylbenzyloxy)-5-methylsulfanyl-phenyl]-vinyl)-nicotinic acid



15 Sodium hydride (160 mg, 60% w/w in mineral oil, 4 mmol) was added to a solution containing 4-isopropylbenzyl chloride (350 μ L, 2.1 mmol) and 6-[E-2-(2-hydroxy-5-methylsulfanylphenyl)-vinyl]-nicotinic acid, methyl ester (600 mg, 2 mmol) in DMF (20 mL). The mixture was stirred overnight at room temperature. The reaction mixture was 20 concentrated *in vacuo* and the residue was dissolved in THF (10 mL). Methanol (4 mL) and aqueous sodium hydroxide (4 mL, 1M) were added and the solution was stirred at room temperature for 5 hours. The reaction mixture was concentrated *in vacuo* before being dissolved in water (10 mL). This solution was acidified with hydrochloric acid (1M) and the resulting precipitate was isolated by filtration, washed with water and dried *in vacuo*. The 25 product was obtained as a yellow solid (880 mg, quant.) δ_H (300 MHz, DMSO- d_6) 13.2 (1H, s), 9.01 (1H, d), 8.22 (1H, dd), 8.04 (1H, d), 7.66 (1H, d), 7.53 (1H, d), 7.45 (1H, d), 7.39 (2H,

d), 7.29-7.20 (3H, m), 7.11 (1H, d), 5.18 (4H, s), 2.87 (1H, septet), 2.51 (3H and residual DMSO-*d*₅, s), and 1.19 (6H, d); ^{m/z} (LCMS) (ESI+) 420 (MH+); (ESI-) 418 (M-H).

EXAMPLE C

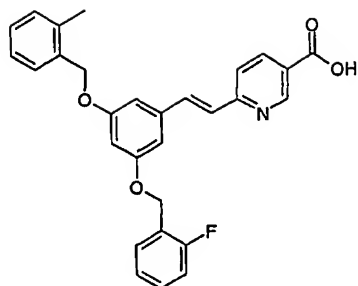
5 Scheme 2: Preparation of 6-[E-2-(-2-hydroxy-5-methylsulfanylphenyl)-vinyl]-nicotinic acid, methyl ester

Sodium methoxide (2.29 g, 42.4 mmol) was added to a suspension of 6-[E-2-(-2-acetoxy-5-methylsulfanylphenyl)-vinyl]-nicotinic acid, methyl ester (13.26g, 38.55 mmol) in methanol (200 mL). The mixture was heated at 60°C for 3 hours. The reaction mixture was concentrated
10 *in vacuo* and water was added followed by enough hydrochloric acid (1M) to acidify the solution. The resultant precipitate was isolated by filtration, washed with water and dried *in vacuo*. This procedure afforded the product as a yellow solid (8.8g, 76%) ^{m/z} (LCMS) (ESI+) 302 (MH+); (ESI-) 300 (M-H).

15 EXAMPLE D

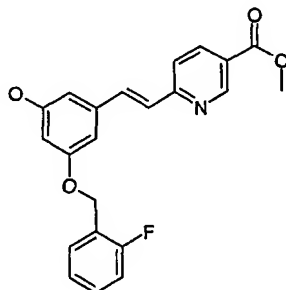
Scheme 2: Preparation of 6-[E-2-(-2-acetoxy-5-methylsulfanylphenyl)-vinyl]-nicotinic acid, methyl ester

2-hydroxy-5-methylsulfanylbenzaldehyde (5.05 g, 30 mmol) was dissolved in acetic anhydride (8 mL). Methyl 6-methylnicotinate (4.54 g, 30 mmol) and acetic acid (1.7 mL, 30 mmol) were
20 added. The mixture was heated to 120°C and stirred for 18 hours. The mixture was allowed to cool to room temperature before being poured into water (200 mL). The aqueous mixture was extracted with ethyl acetate (200 mL). The extract was washed with brine, dried over magnesium sulfate and concentrated *in vacuo* to afford a brown solid. This material was triturated with ethanol to give 6-[E-2-(-2-acetoxy-5-methylsulfanylphenyl)-vinyl]-nicotinic
25 acid, methyl ester as a colourless solid (7.33 g, 71%) δ_H (300 MHz, DMSO-*d*₆) 9.06 (1H, d), 8.28 (1H, dd), 7.77-7.68 (3H, m), 7.50 (1H, d), 7.27 (1H, d), 7.15 (1H, d), 3.86 (3H, s), 2.55 (3H, s), and 2.36 (3H, s); ^{m/z} (ESI+) 344 (MH+).

EXAMPLE E**Scheme 3: Preparation of**

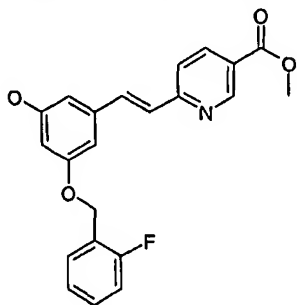
Compound (a) (260mg 0.69mm) was stirred with potassium carbonate (286mg 2.07mm),
 5 potassium iodide (catalytic) and 2-methylbenzyl bromide (0.101ml 0.76mm) in
 dimethylformamide at 60° C overnight.

Compound (a)



10

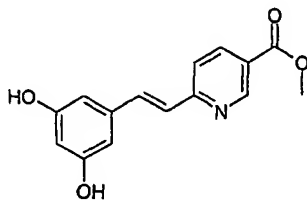
Water (5ml) was added to the cooled reaction and the mixture was filtered, washed well with
 water and dried under vacuum at room temperature. The compound was purified by bond
 elute chromatography, eluting with 20% ethyl acetate/isohexane. The product from this
 column was stirred with 2N sodium hydroxide (1.725ml 3.45mm) in tetrahydrofuran (4ml)
 15 methyl alcohol (2ml) and water (2ml) for 3 hours at room temperature. The mixture was then
 evaporated to dryness, diluted with water and acidified with 2N hydrochloric acid to give a
 precipitate. The precipitate was filtered off, washed well with water and dried at room
 temperature under vacuum to give the product. (270mg 83.4%) Nmr dmso-d₆ (d) 2.34
 (3H s), 5.11-5.23 (4H d) 6.72 (1H s) 7.05 (2H s) 7.15-7.35 (5H m) 7.4-7.5 (3H m) 7.55-7.65
 20 (2H m) 7.68-7.78 (1H d) 8.18-8.23 (1H d) 9.03 (1H s) M.S.- MH⁺ 470.

EXAMPLE F**Scheme 3: Preparation of**

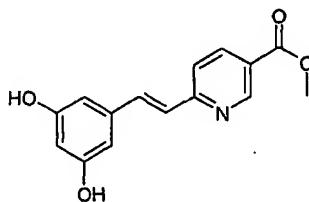
- 5 Compound (b) (9.65g 35.61mm) was stirred with 2-fluorobenzyl bromide (4.29ml 35.61mm), potassium carbonate (14.74g 106.83mm) potassium iodide (1.0g 6mm catalytic) in dimethylformamide (40ml).

Compound (b)

10



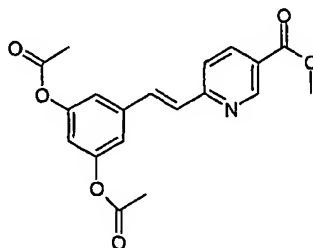
- After cooling, the mixture was poured into water and extracted into ethyl acetate. The combined organic extracts were dried over magnesium sulphate , filtered and evaporated to give the crude product.. Chromatography on silica using 0.6% methanol/methylene chloride, followed by 10% methanol/methylene chloride gave the pure product (1.89g 14%).M.S. MH⁺ 380.

EXAMPLE G**Scheme 3: Preparation of**

20

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The diacetyl derivative (15.36g 43mm) of the the structure above was stirred at room temperature with 4N sodium methoxide (9.8ml 43mm) in tetrahydrofuran (10ml) and methanol (10ml) for 1 hour . The mixture was evaporated diluted with water and acidified with hydrochloric acid .The resulting precipitate was filtered off washed with water and
5 vacuum dried at 50°C to give the product (11.2g 96.1%) MS MH⁺ 272

EXAMPLE H**Scheme 3: Preparation of**

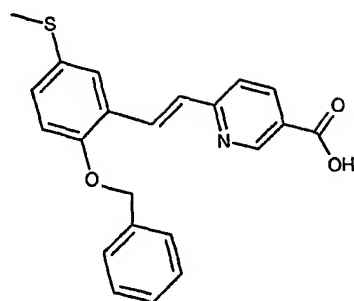
10 3,5-Dihydroxybenzaldehyde (10.0g 72.46mm) was stirred with 6-methyl methyl nicotinate (10.94g 72.46mm) in acetic acid (3.7ml 65mm) and acetic anhydride (37ml 0.39m) at 120°C overnight. On cooling the brown solid mixture was diluted with ethyl acetate .The insoluble material was filtered off and washed with ethyl acetate to give the product (15.36g) The remaining organic solubles were washed with water then added to sodium bicarbonate and the
15 solid filtered off washed with water and vacuum dried(1.78g) .Both the solids were identical and so were combined to give the final product (17.14g 66.6%) MS MH⁺ 356 .

EXAMPLE I**Scheme 4: Preparation of 6-(E-2-[2-(2-benzoyloxy)-5-methylsulfonyl-phenyl]-vinyl)-**

20 **nicotinic acid, methyl sulphonamide**

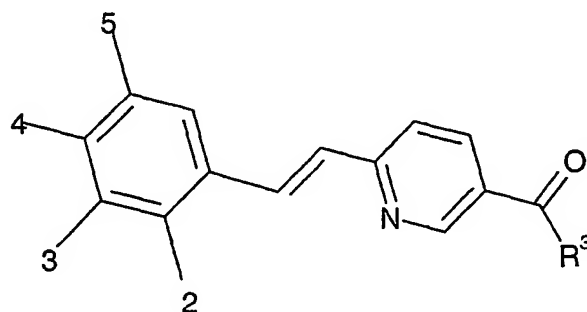
To a suspension of Compound (c) (100mg) in dichloromethane (10ml) was added methanesulfonamide (38mg), 4-dimethylaminopyridine (130mg), then 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (102mg).The mixture was stirred for 20 hours at ambient temperature.Diluted with dichloromethane (20ml), washed with 2M
25 hydrochloric acid (10ml), brine (15ml), and dried over Magnesium sulfate. Volatile material was removed by evaporation to give the title product (112mg), as a solid. ¹HNMR (CDCl₃) 2.48 (s, 3H), 3.43 (s, 3H), 5.20 (s, 2H), 6.92 (d, 1H), 7.25 (m, 1H+CDCl₃), 7.33-7.48 (m, 7H), 7.57 (d, 1H), 7.60 (s, 1H), 8.13 (d, 1H), 8.32 (d,1H), 9.26 (s, 1H). MS ES⁺ 455.13 (M+H)⁺.

Compound (c)



5 EXAMPLE J

By analogous methods to those described compounds J₁₋₁₂₇ listed in Table 1 were also made. Table 2 gives the parent molecular weight, mass spec data and the synthetic scheme for the compounds listed in Table 1.



10

In compounds 1-114 R^3 is OH; in compounds 115-123 R^3 is methoxy; in compound 124 R^3 is methylsulphonylamino; in compound 125 R^3 is methoxyamino; in compounds 126-127 R^3 is 2-hydroxyethylamide.

15 Compound 2 corresponds to the product of Example A. Compound 36 corresponds to the product of Example B. Compound 101 corresponds to Example E. Compound 124 corresponds to the product of Example I.

TABLE 1

Compound number	2	3	4	5
1	H	Methylthio	H	H
2	H	Phenoxy	H	H

Compound number	2	3	4	5
3	H	CF ₃	H	CF ₃
4	H	Benzyloxy	H	H
5	OH	Br	H	Br
6	4-ChloroPhenylthio	H	H	NO ₂
7	4-MethylPhenylthio	H	H	NO ₂
8	Chloro	H	H	Ethoxy
9	Chloro	H	H	Chloro
10	Chloro	H	H	CF ₃
11	H	H	(5-t-Butyl)-thiazol-2-yl	H
12	H	(4-t-Butyl)-Phenoxy	H	H
13	Bromo	H	H	OMe
14	Bromo	H	H	OEt
15	1-morpholino	H	H	NO ₂
16	3-Trifluoromethyl-phenoxy	H	H	NO ₂
17	methoxy	H	H	SMe
18	4-Fluorobenzyloxy	H	H	SMe
19	4-Methoxybenzyloxy	H	H	SMe
20	OH	H	H	SMe
21	OH	H	H	OMe
22	Allyloxy	H	H	SMe
23	Cyclopropyl methoxy	H	H	SMe
24	O-3-Pentyl	H	H	SMe
25	benzyloxy	H	H	OMe
26	Benzyloxy	H	H	SMe
27	H	4-Fluorophenyl	H	H
28	H	4-Chlorophenoxy	H	H
29	H	OMe	H	OMe
30	H	4-Methoxyphenoxy	H	H
31	Fluoro	H	H	Trifluoro-methyl
32	4-ChloroPhenylthio	H	H	H
33	3-Carboxybenzyloxy	H	H	SMe
34	4-Carboxybenzyloxy	H	H	SMe
35	3-Nitrobenzyloxy	H	H	SMe
36	4-Isopropylbenzyloxy	H	H	SMe
37	4-Methylsulphonyl-benzyloxy	H	H	SMe
38	3,5-	H	H	SMe

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Compound number	2	3	4	5
	Difluorobenzyloxy			
39	4-Vinylbenzyloxy	H	H	SMe
40	2,4-Difluorobenzyloxy	H	H	SMe
41	3-Trifluoromethyl-4-fluorobenzyloxy	H	H	SMe
42	3-Trifluoromethylbenzyloxy	H	H	SMe
43	3,4-Methylenedioxybenzyloxy	H	H	SMe
44	3-Fluorobenzyloxy	H	H	SMe
45	2-Methylbenzyloxy	H	H	SMe
46	3-Methylbenzyloxy	H	H	SMe
47	2-Fluorobenzyloxy	H	H	SMe
48	4-Bromobenzyloxy	H	H	SMe
49	4-Methylbenzyloxy	H	H	SMe
50	3-Methoxybenzyloxy	H	H	SMe
51	3,4-Difluorobenzyloxy	H	H	SMe
52	3-Carboxybenzyloxy	H	H	H
53	3,5-Difluorobenzyloxy	H	H	H
54	2-Cyanoobenzyloxy	H	H	H
55	2-Methylbenzyloxy	H	H	H
56	2,4-Difluorobenzyloxy	H	H	H
57	3-Trifluoromethylbenzyloxy	H	H	H
58	2,5-Difluorobenzyloxy	H	H	H
59	3,4-Methylenedioxybenzyloxy	H	H	H
60	3-Fluorobenzyloxy	H	H	H
61	2-Fluorobenzyloxy	H	H	H
62	4-Fluorobenzyloxy	H	H	H
63	3-Methoxybenzyloxy	H	H	H
64	3-Phenylallyloxy	H	H	SMe
65	3-Phenylpropoxy	H	H	SMe
66	Cyclohexylmethoxy	H	H	SMe

Compound number	2	3	4	5
67	2-N-Methylpyrrolidino-2-Ethoxy	H	H	SMe
68	2-(4-Bromophenoxy)-ethoxy	H	H	SMe
69	2-Hydroxy-2-Trifluoromethyl-ethoxy	H	H	SMe
70	4-(3,5-dimethylisoxazolo)-methoxy	H	H	SMe
71	2-(2-1,3-diazolo)-ethoxy	H	H	SMe
72	2-Carboxyfurano-methoxy	H	H	SMe
73	H	2-Chlorobenzoyloxy	H	H
74	Benzoyloxy	H	H	2-Methoxy-ethoxy
75	2-Methylbenzoyloxy	H	H	2-Methoxy-ethoxy
76	Benzoyloxy	H	H	Trifluoro-methoxy
77	3-Methylbenzoyloxy	H	H	Trifluoro-methoxy
78	Hydroxy	H	H	t-Butyl
79	3-(5-methyl)isoxazolo-methoxy	H	H	SMe
80	2-Furanomethoxy	H	H	SMe
81	3-Pyridomethoxy	H	H	SMe
82	2-Thiophenomethoxy	H	H	SMe
83	3-Thiophenomethoxy	H	H	SMe
84	Benzoyloxy	H	H	2-Cyano-benzoyloxy
85	4-Phenylcarbamoyl-benzoyloxy	H	H	SMe
86	4-Carbamoyl-benzoyloxy	H	H	SMe
87	4-benzoyl-benzoyloxy	H	H	SMe
88	4-Sulphamoyl-	H	H	SMe

Compound number	2	3	4	5
	benzyloxy			
89	4-Carboxymethylbenzyloxy	H	H	SMe
90	4-(2-Methylcarboxy)phenylbenzyloxy	H	H	SMe
91	4-Carboxymethoxybenzyloxy	H	H	SMe
92	4-Cyanobenzyloxy	H	H	SMe
93	4-Nitrobenzyloxy	H	H	SMe
94	H	2-Cyanobenzyloxy	H	2-Cyanobenzyloxy
95	H	2-Fluorobenzyloxy	H	2-Fluorobenzyloxy
96	H	2-Chlorobenzyloxy	H	2-Chlorobenzyloxy
97	H	3-(5-methyl)isoxazolylmethoxy	H	3-(5-methyl)isoxazolylmethoxy
98	H	2-[2-methylthiazol-4-yl]ethoxy	H	2-[4-(2-methyl)thiazolyl]ethoxy
99	H	Benzyloxy	H	2-Fluorobenzyloxy
100	H	2-chlorobenzyloxy	H	2-Fluorobenzyloxy
101	H	2-Methylbenzyloxy	H	2-Fluorobenzyloxy
102	H	2-Cyanobenzyloxy	H	2-Fluorobenzyloxy
103	H	2-Trifluoromethylbenzyloxy	H	2-Fluorobenzyloxy
104	H	2-Trifluoromethoxybenzyloxy	H	2-Fluorobenzyloxy
105	H	2-Methoxybenzyloxy	H	2-Fluorobenzyloxy
106	H	2-[2-methylthiazol-4-yl]ethoxy	H	Isopropoxy
107	H	2-[2-methylthiazol-4-yl]ethoxy	H	2-Pyridylmethoxy
108	H	5-methylisoxazol-3-yl-	H	Isopropoxy

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Compound number	2	3	4	5
		methoxy		
109	H	5-methylisoxazol-3-yl-methoxy	H	2-Methyl-benzyloxy
110	H	5-methylisoxazol-3-yl-methoxy	H	4-(2-methyl)-thiazolyl-methoxy
111	H	2-[4-methylthiazol-5-yl]ethoxy	H	2-Methyl-benzyloxy
112	H	2-[4-methylthiazol-5-yl]-ethoxy	H	3-(5-methyl)-isoxazolyl-methoxy
113	4-Isopropylbenzyloxy	H	H	Methyl-sulphoxy
114	Benzyloxy	H	H	Methyl-sulphonyl
115	Ethylthio	Methoxy	H	H
116	Hydroxy	H	H	Methylthio
117	H	2-chlorobenzyloxy	H	H
118	H	2-[4-methylthiazol-5-yl]-ethoxy	H	Isopropoxy
119	H	2-[4-methylthiazol-5-yl]-ethoxy	H	2-Pyridyl-methoxy
120	H	5-methylisoxazol-3-yl-methoxy	H	Isopropoxy
121	H	5-methylisoxazol-3-yl-methoxy	H	2-Methyl-benzyloxy
122	H	5-methylisoxazol-3-yl-methoxy	H	2-[4-(2-methyl)-thiazolyl]-ethoxy
123	H	2-[4-methylthiazol-5-yl]-ethoxy	H	2-Methyl-benzyloxy
124	Benzyloxy	H	H	Methylthio
125	Benzyloxy	H	H	Methylthio
126	Benzyloxy	H	H	Bromo
127	Benzyloxy	H	H	Methylthio

TABLE 2

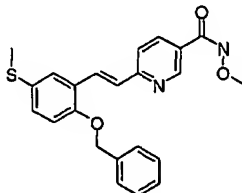
Compound Number	Parent Molecular Weight	Mass Spec (+ve / -ve)	Synthetic scheme
1	271.34	272,	1
2	317.35	318,	1
3	361.25	362,	1
4	331.37	332,	1
5	399.04	398,400,402,	1
6	412.85	411,413	1
7	392.44	391,393	1
8	303.75	302,304	1
9	294.14	295,293	1
10	327.69	326,328	1
11	364.47	365,363	1
12	373.46	374,372	1
13	334.17	334,336	1
14	348.2	348,350	1
15	355.35	354,356	1
16	430.34	431,	1
17	301.37	302,300	2
18	395.46	396,394	2
19	407.49	408,406	2
20	287.34	288,286	2
21	271.28	272,270	2
22	327.41	328,	2
23	341.43	342,	2
24	357.48	358,	2
25	361.4	362,360	2
26	377.47	378,376	2
27	319.34	320,318	2
28	351.79	352,350	2
29	285.3	286,284	2
30	347.37	348,346	2
31	311.24	312,310	2
32	367.86	368,366	2
33	421.48	422,	2
34	421.48	422,420	2
35	422.46	423,421	2
36	419.55	420,418	2
37	455.56	456,454	2
38	413.45	414,412	2
39	403.5	404,402	2
40	413.45	414,412	2
41	463.45	464,462	2
42	445.46	446,444	2

- 50 -

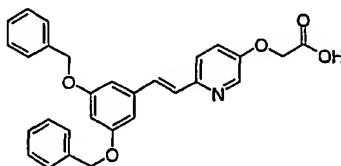
Compound Number	Parent Molecular Weight	Mass Spec (+ve / -ve)	Synthetic scheme
43	421.48	422,420	2
44	395.46	396,394	2
45	391.49	392,390	2
46	391.49	392,390	2
47	395.46	396,394	2
48	456.36	456,458,454,456	2
49	391.49	392,390	2
50	407.49	408,406	2
51	413.45	414,412	2
52	375.38	376,374	2
53	367.36	368,366	2
54	356.38	357,355	2
55	345.4	346,344	2
56	367.36	368,366	2
57	399.37	400,398	2
58	367.36	368,366	2
59	375.38	376,374	2
60	349.36	350,348	2
61	349.36	350,348	2
62	349.36	350,348	2
63	361.4	362,360	2
64	403.5	404,402	2
65	405.52	406,404	2
66	383.51	384,382	2
67	398.53	399,397	2
68	486.39	486,488,484,486	2
69	399.39	400,398	2
70	396.47	397,395	2
71	387.46	388,386	2
72	411.44	412,410	2
73	365.82	366,	2
74	405.45	406	2
75	419.48	420	2
76	415.37	416	2
77	429.4	430	2
78	297.36	298,296	2
79	382.44	383,	2
80	367.43	368,	2
81	378.45	379,	2
82	383.49	384,	2
83	383.49	384,	2
84	462.51	463	2

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Compound Number	Parent Molecular Weight	Mass Spec (+ve / -ve)	Synthetic scheme
85	496.59	497	2
86	420.49	421	2
87	481.57	482	2
88	456.54	457	2
89	435.5	436	2
90	511.6	512	2
91	451.5	452	2
92	402.48	403	2
93	422.46	423	2
94	487.52	488	2
95	473.48	474,	2
96	506.39	506,	2
97	447.45	448,446	2
98	507.63	508,	2
99	455.49	456,454	3
100	489.94	490,492,488,490	3
101	469.52	470,68	3
102	480.5	481,479	3
103	523.49	524,522	3
104	539.49	540,538	3
105	485.52	486,484	3
106	424.52	425,423	3
107	473.55	474,472	3
108	394.43	395,393	3
109	456.5	457,455	3
110	463.52	464,462	3
111	486.59	487,485	3
112	477.54	478,476	3
113	435.55	434,436	5
114	409.464	,408	5
115	329.42	330,	1
116	301.37	302,300	2
117	379.85	380,	2
118	438.55	439,	3
119	487.58	488,	3
120	408.46	409,	3
121	470.53	471,469	3
122	477.54	478,476	3
123	500.62	501,499	3
124	454.57	455.13	4
125	406.51	407.12	4
126	453.339	453,	4
127	420.534	421,	4

EXAMPLE K**Scheme 5 : Preparation of 6-(E-2-[-2-(2-benzyloxy)-5-methylsulfanyl-phenyl]-vinyl)-nicotinic acid, N-methoxyamide.**

- 5 To a stirred suspension of 6-{(E)-2-[2-(benzyloxy)-5-(methylthio)phenyl]ethenyl}nicotinic acid (82 mg, 0.22 mmol) in DCM (10 ml) was added oxalyl chloride (35 mg, 0.28 mmol) and DMF (catalytic amount). The mixture was stirred at ambient temperature for 17 hours, and volatile material removed by evaporation to give a gum which was then suspended in DCM (10 ml). Methoxyamine hydrochloride (37 mg, 0.44 mmol) and triethylamine (0.06 ml, 0.43
- 10 mmol) were added to the suspension and the resulting solution stirred at ambient temperature for 4 hours. It was then diluted with DCM (20 ml) and washed sequentially with 2M hydrochloric acid (20 ml), brine (20 ml), and dried over MgSO₄. Volatile material was removed by evaporation to leave a gum which was purified by flash chromatography on silica, eluting with 1-2% methanol in DCM to give an oil. Triturated with diethyl ether gave 6-(E-2-
- 15 [-2-(2-benzyloxy)-5-methylsulfanyl-phenyl]-vinyl)-nicotinic acid, N-methoxyamide (33 mg) as a solid, NMR: δ_H (300MHz, DMSO-d₆) 2.48 (s, 3H+DMSO), 3.72 (s, 3H), 5.22 (s, 2H), 7.11 (d, 1H), 7.24 (s, 1H), 7.30-7.53 (m, 7H), 7.68 (s, 1H), 8.05 (m, 2H), 8.88 (s, 1H), 11.82 (s, 1H); m/z 407 (M+H)⁺.

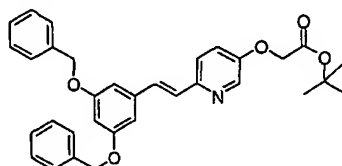
20 EXAMPLE L**Scheme 6 : Preparation of 6-(E-2-[-2-(3,5-dibenzyloxy)-phenyl]-vinyl)-pyridine-3-oxyacetic acid.**

- To a stirred solution of 6-(E-2-[-2-(3,5-dibenzyloxy)-phenyl]-vinyl)-pyridine-3-oxyacetic acid
- 25 t-butyl ester (100 mg, 0.19 mmol) in dichloromethane (2 ml) was added trifluoroacetic acid (1 ml). The solution was stirred at ambient temperature for 6 hours. Volatile material was removed by evaporation, and the residue azeotroped with toluene to give an oil. This was

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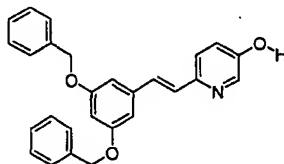
trituated under diethyl ether to give the title compound (72 mg) as a solid, NMR: δ_H (300MHz, DMSO- d_6) 4.80 (s, 2H), 5.12 (s, 4H), 6.60 (s, 1H), 6.89 (s, 2H), 7.08-7.60 (m, 14H), 8.31 (s, 1H), m/z 468 (M+H)⁺.

5 The requisite t-butyl ester starting material was prepared as follows:



To a suspension of 3-hydroxy-6-(E-2-[-2-(3,5-dibenzyloxy)-phenyl]-vinyl) pyridine (150 mg) in anhydrous THF (10 ml) was added sodium hydride (30mg) at ambient temperature, under an atmosphere of nitrogen. The reaction was allowed to stir for 20 minutes and then t-butyl
 10 bromo acetate (0.06 ml) was added. The reaction was stirred for 30 minutes before being cooled to 0°C and DMF (3 ml) added. The reaction was then allowed to warm to ambient temperature, when water (20 ml) was added. The aqueous was extracted with ethyl acetate (3x 20 ml) and the extracts combined, dried (MgSO₄) and evaporated to leave an oil. This was
 15 purified by flash chromatography on a 10g silica Bondelut, to give an oil which was trituated under diethyl ether:hexane (1:1) to give 6-(E-2-[-2-(3,5-dibenzyloxy)-phenyl]-vinyl)-pyridine-3-oxyacetic acid t-butyl ester (135 mg) as a solid, MS m/z 524 (M+H)⁺.

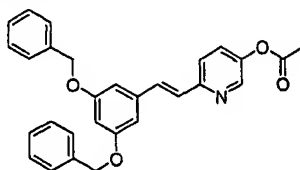
The requisite 3-hydroxy pyridine starting material was prepared as follows:



To a suspension of 3-acetoxy-6-(E-2-[-2-(3,5-dibenzyloxy)-phenyl]-vinyl) pyridine (100 mg) in methanol (2 ml) was added sodium hydroxide (0.44ml, 0.86mmol), and the mixture stirred at ambient temperature for 1.5 hours. An excess of 2M hydrochloric acid was added. A precipitate formed, which was filtered off, washed sequentially with water and ether, and dried under vacuum at 60°C for 5 hours, to give 3-hydroxy-6-(E-2-[-2-(3,5-dibenzyloxy)-
 25 phenyl]-vinyl) pyridine (82 mg) as a solid, m/z 410 (M+H)⁺.

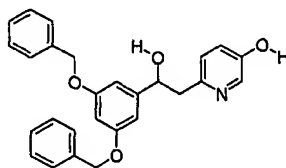
- 54 -

The requisite 3-acetoxy pyridine starting material was prepared as follows:

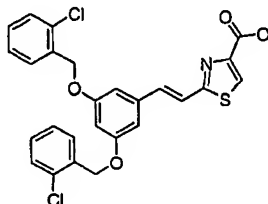


To a stirred solution of 6-{2-[3,5-bis(benzyloxy)phenyl]-2-hydroxyethyl}pyridin-3-ol (105 mg) in acetic anhydride (0.23 ml) was added acetic acid (0.23 ml); the mixture was heated to 120°C and stirred for 17 hours. It was then allowed to cool to ambient temperature and water (10 ml) was added, followed by extraction with ethyl acetate (3x 20 ml). The extracts were combined, dried (MgSO₄) and evaporated to give an oil, which was triturated under hexane to give the title compound (80 mg) as a solid. MS ES⁺ 452 (M+H)⁺.

10 The requisite 6-{2-[3,5-bis(benzyloxy)phenyl]-2-hydroxyethyl}pyridin-3-ol starting material was prepared as follows:

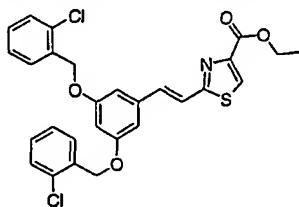


To a stirred solution of 5-{[*tert*-butyl(dimethyl)silyl]oxy}-2-methyl pyridine (1.20 g) in anhydrous THF (15 ml) under nitrogen and at -78°C was added LDA (3.22 ml), and the solution stirred at -78°C for 1 hour. 3,5 dibenzyloxy-benzaldehyde (2.05 g) was then added dropwise as a solution in THF, and the reaction mixture allowed to warm to ambient temperature over 1 hour. Water (20 ml) was added and the resulting mixture extracted with ethyl acetate (3x30 ml). The extracts were combined, washed with brine (20 ml), dried (MgSO₄) and evaporated to give a gum. This was dissolved in THF (10 ml) and concentrated hydrochloric acid (10 ml) added. The mixture was stirred at ambient temperature for 3 hours, cooled to 0°C and taken to pH 8.5 with concentrated ammonia solution. The mixture was diluted with water (50 ml) and extracted with ethyl acetate (3x100 ml). The extracts were combined, dried (MgSO₄) and evaporated to leave an oil which was purified by MPLC on silica, eluting with 60-100% ethyl acetate in hexane to give 6-{2-[3,5-bis(benzyloxy)phenyl]-2-hydroxyethyl}pyridin-3-ol (2.25 g) as a glass, m/z 428 (M+H)⁺.

EXAMPLE M**Scheme 7 : Preparation of E 2-{-2-[3,5-di-(2-chlorobenzoyloxy)]-phenyl}-vinyl-thiazole-4-carboxylic acid.**

- 5 This was prepared from E 2-{-2-[3,5-di-(2-chlorobenzoyloxy)]-phenyl}-vinyl-thiazole-4-carboxylic acid ethyl ester by alkaline hydrolysis in a manner similar to that described in Example A, Scheme 1.

The requisite ethyl ester starting material was prepared as follows:

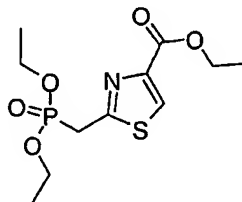


10

- Ethyl 2-[(diethoxyphosphoryl)methyl]-1,3-thiazole-4-carboxylate (280 mgs, 0.91 mmol) in dry tetrahydrofuran (10ml) was added to a stirred suspension of sodium hydride (40mgs of 60% dispersion, 1 mmol) in dry tetrahydrofuran (10ml). After stirring for half an hour at room temperature a solution of 3,5 bis (2-chlorobenzyl)benzaldehyde (420 mgs 1.09 mmol) in dry tetrahydrofuran (10ml) was added slowly. The mixture was stirred at ambient temperature for 15 4 hours, quenched with water and acidified with 2M aq hydrochloric acid. The mixture was extracted with ethyl acetate and the extrac combined, dried (MgSO₄) and evaporated to leave a gum. Chromatography on silica, eluting with 20% EtOAc in hexane, gave E 2-{-2-[3,5-di-(2-chlorobenzoyloxy)]-phenyl}-vinyl-thiazole-4-carboxylic acid ethyl ester (260mgs), NMR: δ_H (300MHz, DMSO-d₆): 1.25-1.35(3H,t); 4.25-4.35 (2H, q); 5.2 (4H, s); 6.69 (1H, s); 7.08 (2H,s); 7.34-7.45 (4H, m); 7.45-7.55 (3H,m); 7.55-7.65 (3H,m); 8.45 (1H, m). 20

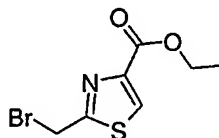
- 56 -

The requisite ethyl 2-[(diethoxyphosphoryl)methyl]-1,3-thiazole-4-carboxylate starting material was prepared as follows:



Ethyl 2-(bromomethyl)-1,3-thiazole-5-carboxylate (460mgs, 1.85 mmol) in dry
 5 tetrahydrofuran (2.5ml) was added dropwise to triethylphosphite (2.5ml, 2.46g, 14.8 mmol)
 under argon at a temperature of 105°C. On completion of the addition the mixture was
 warmed to 140°C at which it was maintained for one hour. The triethylphosphite was then
 removed under reduced pressure and the resultant material chromatographed (silica,
 EtOAc/hexane) to give ethyl 2-[(diethoxyphosphoryl)methyl]-1,3-thiazole-4-carboxylate (300
 10 mgs), NMR: δ_H (300MHz, DMSO- d_6): 1.15-1.35 (9H,m); 3.95-4.12 (4H,m); 4.22-4.35 (2H,q);
 8.43 (1H,s).

The requisite ethyl 2-(bromomethyl)-1,3-thiazole-5-carboxylate starting material was prepared as follows:

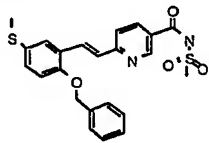
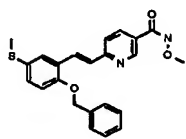
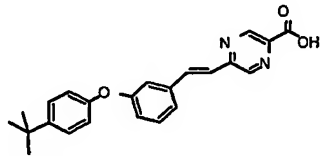
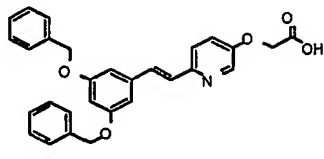
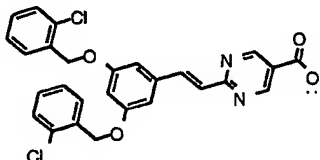


15 N- Bromosuccinimide (0.91g, 5.1 mmol) was added to a solution of ethyl 2-methyl-thiazole-
 5-carboxylate (0.8g, 4.7 mmol) in carbon tetrachloride. The resultant reaction mixture was
 stirred for one hour whilst being illuminated by a photoflood lamp. After removing the solvent
 from the reaction mixture the resultant material was partitioned between ethyl acetate and
 20 water. The organic phase was then separated off, dried (MgSO₄) and the evaporated.
 Chromatography on silica, eluting with 30% ethyl acetate in hexane, gave ethyl 2-
 (bromomethyl)-1,3-thiazole-5-carboxylate (490 mgs), NMR: δ_H (300MHz, DMSO- d_6 : 1.20-
 1.38 (3H,t); 4.20-4.37 (2H, q); 5.05 (2H, s); 8.55 (1H, s).

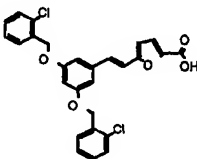
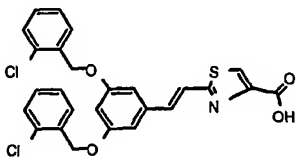
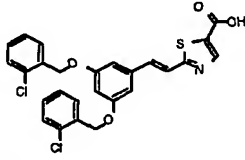
EXAMPLE N

By analogous methods to those described compounds N₁₋₈ listed in Table 3 were also made.

TABLE 2

No	Structure	Route (Example)	MS	NMR
1	 <p>E FORM</p>	I	455	δ_H (300MHz, CDCl ₃) 2.48 (s, 3H), 3.43 (s, 3H), 5.20 (s, 2H), 6.92 (d, 1H), 7.25 (s, CHCl ₃ +1H), 7.33-7.48 (m, 7H), 7.57 (d, 1H), 7.60 (s, 1H), 8.13 (d, 1H), 8.32 (d, 1H), 9.26 (s, 1H).
2	 <p>E FORM</p>	K Scheme 5	407	δ_H (300MHz, DMSO-d ₆) 2.48 (s, 3H+DMSO), 3.72 (s, 3H), 5.22 (s, 2H), 7.11 (d, 1H), 7.24 (s, 1H), 7.30-7.53 (m, 7H), 7.68 (s, 1H), 8.05 (m, 2H), 8.88 (s, 1H), 11.82 (s, 1H).
3	 <p>E FORM</p>	A Scheme 1	373	δ_H (300MHz, DMSO-d ₆) 1.2 (s, 9H), 7.0 (d, 3H), 7.4 (m, 6H), 7.8 (d, 1H), 8.7 (s, 1H), 9.1 (s, 1H).
4	 <p>E FORM</p>	L Scheme 6	468	δ_H (300MHz, DMSO-d ₆) 4.80 (s, 2H), 5.12 (s, 4H), 6.60 (s, 1H), 6.89 (s, 2H), 7.08-7.60 (m, 14H), 8.31 (s, 1H).
5	 <p>E FORM</p>	A Scheme1*		δ_H (300MHz, DMSO-d ₆) 5.21 (4H, s), 6.72 (1H, s), 7.10 (2H, app s), 7.30-7.44 (5 H, m), 7.44-7.55 (2H, m), 7.55-7.65 (2, m), 7.90-8.1 (1H, d), 9.14 (2H, s).

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6	 E FORM	M Scheme 7 (by analogy with Example 8)		δ_H (300MHz, DMSO- d_6) 5.20 (4H, s), 6.62 (1H, s), 6.71 (1H, d), 6.97 (2H, d), 7.14 (1H, d), 7.26 (2H, m), 7.40 (4H, m), 7.52 (2H, m), 7.63 (2H,m).
7	 E FORM	M Scheme 7 (by analogy with Example 8)	512 514	δ_H (300MHz, DMSO- d_6), 5.19 (4H,s), 6.68 (1H, s), 7.01 (2H, s), 7.31-7.45 (5, m), 7.45-7.58 (~2.5H, m), 7.58-7.69 (~2.5H, m), 7.87 (1H, s)
8	 E FORM	M Scheme 7 ** (described)	512	δ_H (300MHz, DMSO- d_6), 5.19 (4H, s), 6.72 (1H, s), 7.08 (2H, s), 7.30-7.45 (4H, m), 7.45-7.55 (2H, m), 7.55-7.68 (4H,m), 8.33 (1H, s)

* Example 5 – starting material (ethyl 2-methyl pyrimidine-5-carboxylate) prepared according to J Het Chem 27 295 (1990).

** Ethyl 2 methyl-1,3-thiazole-5-carboxylate prepared as described in J. Am. Chem. Soc.

5 1982, 104, 4461-4465

The compounds A-I, J₁₋₁₂₇, K, L, M and N₁₋₈ were found to have an activity of at least 40% activity at 10 μ m when tested in the GLK/GLKRP scintillation proximity assay described below.

10

BIOLOGICAL

Tests:

The biological effects of the compounds of the invention may be tested in the following way:

15

(1) Enzymatic activity of GLK may be measured by incubating GLK, ATP and glucose. The rate of product formation may be determined by coupling the assay to a G-6-P dehydrogenase, NADP/NADPH system and measuring the increase in optical density at 340nm (Matschinsky et al 1993).

(2) A GLK/GLKRP binding assay for measuring the binding interactions between GLK and GLKRP. The method may be used to identify compounds which modulate GLK by modulating the interaction between GLK and GLKRP. GLKRP and GLK are incubated with an inhibitory concentration of F-6-P, optionally in the presence of test compound, and the
5 extent of interaction between GLK and GLKRP is measured. Compounds which either displace F-6-P or in some other way reduce the GLK/GLKRP interaction will be detected by a decrease in the amount of GLK/GLKRP complex formed. Compounds which promote F-6-P binding or in some other way enhance the GLK/GLKRP interaction will be detected by an increase in the amount of GLK/GLKRP complex formed. A specific example of such a
10 binding assay is described below

GLK/GLKRP scintillation proximity assay

Recombinant human GLK and GLKRP were used to develop a "mix and measure" 96 well SPA (scintillation proximity assay). (A schematic representation of the assay is given in
15 Figure 3). GLK (Biotinylated) and GLKRP are incubated with streptavidin linked SPA beads (Amersham) in the presence of an inhibitory concentration of radiolabelled [3H]F-6-P (Amersham Custom Synthesis TRQ8689), giving a signal as depicted in Figure 3. Compounds which either displace the F-6-P or in some other way disrupt the GLK / GLKRP binding interaction will cause this signal to be lost.

20 Binding assays were performed at room temperature for 2 hours. The reaction mixtures contained 50mM Tris-HCl (pH = 7.5), 2mM ATP, 5mM MgCl₂, 0.5mM DTT, recombinant biotinylated GLK (0.1 mg), recombinant GLKRP (0.1 mg), 0.05mCi [3H] F-6-P (Amersham) to give a final volume of 100ml. Following incubation, the extent of GLK/GLKRP complex formation was determined by addition of 0.1mg/well avidin linked
25 SPA beads (Amersham) and scintillation counting on a Packard TopCount NXT.

The exemplified compounds described above were found to have an activity of at least 40% activity at 10 μ m when tested in the GLK/GLKRP scintillation proximity assay.

30 (3) A F-6-P / GLKRP binding assay for measuring the binding interaction between GLKRP and F-6-P. This method may be used to provide further information on the mechanism of action of the compounds. Compounds identified in the GLK/GLKRP binding

- 60 -

assay may modulate the interaction of GLK and GLKRP either by displacing F-6-P or by modifying the GLK/GLKRP interaction in some other way. For example, protein-protein interactions are generally known to occur by interactions through multiple binding sites. It is thus possible that a compound which modifies the interaction between GLK and GLKRP could act by binding to one or more of several different binding sites.

The F-6-P / GLKRP binding assay identifies only those compounds which modulate the interaction of GLK and GLKRP by displacing F-6-P from its binding site on GLKRP.

GLKRP is incubated with test compound and an inhibitory concentration of F-6-P, in the absence of GLK, and the extent of interaction between F-6-P and GLKRP is measured. Compounds which displace the binding of F-6-P to GLKRP may be detected by a change in the amount of GLKRP/F-6-P complex formed. A specific example of such a binding assay is described below

F-6-P / GLKRP scintillation proximity assay

Recombinant human GLKRP was used to develop a "mix and measure" 96 well scintillation proximity assay. (A schematic representation of the assay is given in Figure 4). FLAG-tagged GLKRP is incubated with protein A coated SPA beads (Amersham) and an anti-FLAG antibody in the presence of an inhibitory concentration of radiolabelled [3H]F-6-P. A signal is generated as depicted in Figure 4. Compounds which displace the F-6-P will cause this signal to be lost. A combination of this assay and the GLK/GLKRP binding assay will allow the observer to identify compounds which disrupt the GLK/GLKRP binding interaction by displacing F-6-P.

Binding assays were performed at room temperature for 2 hours. The reaction mixtures contained 50mM Tris-HCl (pH = 7.5), 2mM ATP, 5mM MgCl₂, 0.5mM DTT, recombinant FLAG tagged GLKRP (0.1 mg), Anti-Flag M2 Antibody (0.2mg) (IBI Kodak), 0.05mCi [3H] F-6-P (Amersham) to give a final volume of 100ml. Following incubation, the extent of F-6-P/GLKRP complex formation was determined by addition of 0.1mg/well protein A linked SPA beads (Amersham) and scintillation counting on a Packard TopCount NXT.

Production of recombinant GLK and GLKRP:*Preparation of mRNA*

Human liver total mRNA was prepared by polytron homogenisation in 4M guanidine isothiocyanate, 2.5mM citrate, 0.5% Sarkosyl, 100mM b-mercaptoethanol, followed by centrifugation through 5.7M CsCl, 25mM sodium acetate at 135,000g (max) as described in Sambrook J, Fritsch EF & Maniatis T, 1989.

Poly A⁺ mRNA was prepared directly using a FastTrack™ mRNA isolation kit (Invitrogen).

10

PCR amplification of GLK and GLKRP cDNA sequences

Human GLK and GLKRP cDNA was obtained by PCR from human hepatic mRNA using established techniques described in Sambrook, Fritsch & Maniatis, 1989. PCR primers were designed according to the GLK and GLKRP cDNA sequences shown in Tanizawa et al 1991 and Bonthron, D.T. *et al* 1994 (later corrected in Warner, J.P. 1995).

Cloning in Bluescript II vectors

GLK and GLKRP cDNA was cloned in E. coli using pBluescript II, (Short et al 1998) a recombinant cloning vector system similar to that employed by Yanisch-Perron *C et al* (1985), comprising a colEI-based replicon bearing a polylinker DNA fragment containing multiple unique restriction sites, flanked by bacteriophage T3 and T7 promoter sequences; a filamentous phage origin of replication and an ampicillin drug resistance marker gene.

Transformations

E. Coli transformations were generally carried out by electroporation. 400 ml cultures of strains DH5a or BL21(DE3) were grown in L-broth to an OD 600 of 0.5 and harvested by centrifugation at 2,000g. The cells were washed twice in ice-cold deionised water, resuspended in 1ml 10% glycerol and stored in aliquots at -70°C. Ligation mixes were desalted using Millipore V series™ membranes (0.0025mm) pore size). 40ml of cells were incubated with 1ml of ligation mix or plasmid DNA on ice for 10 minutes in 0.2cm electroporation cuvettes, and then pulsed using a Gene Pulser™ apparatus (BioRad) at

30

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0.5kVcm⁻¹, 250mF, 250 ?. Transformants were selected on L-agar supplemented with tetracycline at 10mg/ml or ampicillin at 100mg/ml.

Expression

- 5 GLK was expressed from the vector pTB375NBSE in E.coli BL21 cells,, producing a recombinant protein containing a 6-His tag immediately adjacent to the N-terminal methionine. Alternatively, another suitable vector is pET21(+)DNA, Novagen, Cat number 697703. The 6-His tag was used to allow purification of the recombinant protein on a column packed with nickel-nitrilotriacetic acid agarose purchased from Qiagen (cat no 30250).
- 10 GLKRP was expressed from the vector pFLAG CTC (IBI Kodak) in E.coli BL21 cells, producing a recombinant protein containing a C-terminal FLAG tag. The protein was purified initially by DEAE Sepharose ion exchange followed by utilisation of the FLAG tag for final purification on an M2 anti-FLAG immunoaffinity column purchased from Sigma-Aldrich (cat no. A1205).

15

Biotinylation of GLK:

- GLK was biotinylated by reaction with biotinamidocaproate N-hydroxysuccinimide ester (biotin-NHS) purchased from Sigma-Aldrich (cat no. B2643). Briefly, free amino groups of the target protein (GLK) are reacted with biotin-NHS at a defined molar ratio forming
- 20 stable amide bonds resulting in a product containing covalently bound biotin. Excess, non-conjugated biotin-NHS is removed from the product by dialysis. Specifically, 7.5mg of GLK was added to 0.31mg of biotin-NHS in 4mL of 25mM HEPES pH = 7.3, 0.15M KCl, 1mM dithiothreitol, 1mM EDTA, 1mM MgCl₂ (buffer A). This reaction mixture was dialysed against 100mL of buffer A containing a further 22mg of biotin-NHS. After 4hours excess
- 25 biotin-NHS was removed by extensive dialysis against buffer A.

PHARMACEUTICAL COMPOSITIONS

- The following illustrate representative pharmaceutical dosage forms of the invention as
- 30 defined herein (the active ingredient being termed "Compound X"), for therapeutic or prophylactic use in humans:

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5	(a)	<u>Tablet I</u>	<u>mg/tablet</u>
		Compound X.....	100
		Lactose Ph.Eur.....	182.75
		Croscarmellose sodium.....	12.0
		Maize starch paste (5% w/v paste).....	2.25
		Magnesium stearate.....	3.0
10	(b)	<u>Tablet II</u>	<u>mg/tablet</u>
		Compound X.....	50
		Lactose Ph.Eur.....	223.75
		Croscarmellose sodium.....	6.0
		Maize starch.....	15.0
		Polyvinylpyrrolidone (5% w/v paste).....	2.25
15		Magnesium stearate.....	3.0
	(c)	<u>Tablet III</u>	<u>mg/tablet</u>
		Compound X.....	1.0
		Lactose Ph.Eur.....	93.25
		Croscarmellose sodium.....	4.0
		Maize starch paste (5% w/v paste).....	0.75
20		Magnesium stearate.....	1.0
	(d)	<u>Capsule</u>	<u>mg/capsule</u>
		Compound X.....	10
		Lactose Ph.Eur.....	488.5
25		Magnesium.....	1.5
	(e)	<u>Injection I</u>	<u>(50 mg/ml)</u>
		Compound X.....	5.0% w/v
		1M Sodium hydroxide solution.....	15.0% v/v
		0.1M Hydrochloric acid (to adjust pH = to 7.6)	
		Polyethylene glycol 400.....	4.5% w/v
30		Water for injection to 100%	

5	(f)	<u>Injection II</u>	(10 mg/ml)
		Compound X.....	1.0% w/v
		Sodium phosphate BP.....	3.6% w/v
		0.1M Sodium hydroxide solution.....	15.0% v/v
		Water for injection to 100%	
10	(g)	<u>Injection III</u>	(1mg/ml, buffered to pH = 6)
		Compound X.....	0.1% w/v
		Sodium phosphate BP.....	2.26% w/v
		Citric acid.....	0.38% w/v
		Polyethylene glycol 400.....	3.5% w/v
		Water for injection to 100%	
15	(h)	<u>Aerosol I</u>	<u>mg/ml</u>
		Compound X.....	10.0
		Sorbitan trioleate.....	13.5
		Trichlorofluoromethane.....	910.0
		Dichlorodifluoromethane.....	490.0
20	(i)	<u>Aerosol II</u>	<u>mg/ml</u>
		Compound X.....	0.2
		Sorbitan trioleate.....	0.27
		Trichlorofluoromethane.....	70.0
		Dichlorodifluoromethane.....	280.0
25		Dichlorotetrafluoroethane.....	1094.0
30	(j)	<u>Aerosol III</u>	<u>mg/ml</u>
		Compound X.....	2.5
		Sorbitan trioleate.....	3.38
		Trichlorofluoromethane.....	67.5
		Dichlorodifluoromethane.....	1086.0
		Dichlorotetrafluoroethane.....	191.6

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	(k)	<u>Aerosol IV</u>	<u>mg/ml</u>
		Compound X.....	2.5
		Soya lecithin.....	2.7
5		Trichlorofluoromethane.....	67.5
		Dichlorodifluoromethane.....	1086.0
		Dichlorotetrafluoroethane.....	191.6
	(l)	<u>Ointment</u>	<u>ml</u>
10		Compound X.....	40 mg
		Ethanol.....	300 µl
		Water.....	300 µl
		1-Dodecylazacycloheptan-2-one.....	50 µl
		Propylene glycol.....	to 1 ml

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Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate. The aerosol formulations (h)-(k) may be used in conjunction with standard, metered dose aerosol dispensers, and the suspending agents sorbitan trioleate and soya lecithin may be replaced by an alternative suspending agent such as sorbitan monooleate, sorbitan sesquioleate, polysorbate 80, polyglycerol oleate or oleic acid.

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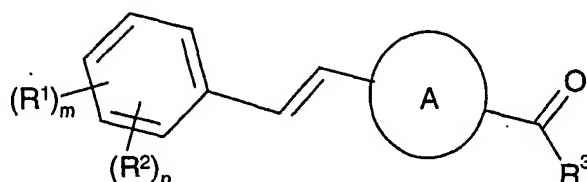
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CLAIMS:

1. The use of a compound of Formula (I) or a salt, solvate or prodrug thereof, in the preparation of a medicament for use in the treatment or prevention of a disease or
 5 medical condition mediated through GLK:



Formula (I)

wherein

A is heteroaryl;

10 **m** is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;

and **n + m** > 0;

each **R¹** is independently selected from OH, $-(CH_2)_{1-4}OH$, $-CH_3-aF_a$, $-(CH_2)_{1-4}CH_3-aF_a$,
 $-OCH_3-aF_a$, halo, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, NO_2 , NH_2 ,
 15 $-NH-C_{1-4}alkyl$, $-N-di-(C_{1-4}alkyl)$, CN , formyl, phenyl or heterocyclyl
 optionally substituted by $C_{1-6}alkyl$;

each **R²** is the group **Y-X-**

wherein each **X** is a linker independently selected from:

-Z-, -O-Z-, -O-Z-O-Z-, -C(O)O-Z-, -OC(O)-Z-, -S-Z-, -SO-Z-, -SO₂-Z-,
 20 -N(R⁷)-Z-, -N(R⁷)SO₂-Z-, -SO₂N(R⁷)-Z-, $-(CH_2)_{1-4}-$, $-CH=CH-Z-$, $-C\equiv C-Z-$,
 $-N(R^7)CO-Z-$, $-CON(R^7)-Z-$, $-C(O)N(R^7)S(O)_2-Z-$, $-S(O)_2N(R^7)C(O)-Z-$,
 $-C(O)-Z-$ or a direct bond;

each **Z** is independently a direct bond, $C_{2-6}alkenylene$ or a group of the formula

$-(CH_2)_p-C(R^7)_2-(CH_2)_q-$;

25 each **Y** is independently selected from aryl-Z¹-, heterocyclyl-Z¹-,

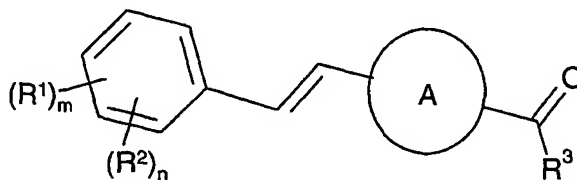
$C_{3-7}cycloalkyl-Z^1-$, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $-(CH_2)_{1-4}CH_3-aF_a$ or
 $-CH(OH)CH_3-aF_a$; wherein each **Y** is independently optionally substituted by
 up to 3 **R⁴** groups;

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- each R^4 is independently selected from halo, $-CH_3-aF_a$, CN, NO_2 , NH_2 , $C_{1-6}alkyl$, $-OC_{1-6}alkyl$, $-COOH$, $-C(O)OC_{1-6}alkyl$, OH or phenyl optionally substituted by $C_{1-6}alkyl$ or $-C(O)OC_{1-6}alkyl$, or R^5-X^1 , where X^1 is independently as defined in X above and R^5 is selected from hydrogen, $C_{1-6}alkyl$, $-CH_3-aF_a$, phenyl, naphthyl, heterocyclyl or $C_{3-7}cycloalkyl$; and R^5 is optionally substituted by halo, $C_{1-6}alkyl$, $-CH_3-aF_a$, CN, NO_2 , NH_2 , $COOH$, or $-C(O)OC_{1-6}alkyl$, wherein each phenyl, naphthyl or heterocyclyl ring in R^5 is optionally substituted by halo, CH_3-aF_a , CN, NO_2 , NH_2 , $C_{1-6}alkyl$, $-OC_{1-6}alkyl$, $COOH$, $-C(O)OC_{1-6}alkyl$ or OH;
- each Z^1 is independently a direct bond, $C_{2-6}alkenylene$ or a group of the formula $-(CH_2)_p-C(R^6)_2-(CH_2)_q$;
- R^3 is selected from OH, $-O-C_{1-6}alkyl$ or NHR^6 ;
- R^6 is selected from hydrogen, $C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, $-SO_2C_{1-6}alkyl$, $-(CH_2)_{0-3}OH$;
- R^7 is independently selected from hydrogen, $C_{1-6}alkyl$ or $-C_{2-4}alkyl-O-C_{1-4}alkyl$;
- each a is independently 1, 2 or 3;
- p is an integer between 0 and 2;
- q is an integer between 0 and 2;
- and $p + q < 4$.

2. A pharmaceutical composition comprising a compound of Formula (I) as claimed in claim 1, or a salt, solvate or prodrug thereof, together with a pharmaceutically-acceptable diluent or carrier for use in the preparation of a medicament for use in the treatment or prevention of a disease or medical condition mediated through GLK.

3. A compound of Formula (Ib) or a salt, solvate or prodrug thereof



Formula (I)

wherein

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A is heteroaryl;

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;

and $n + m > 0$;

5 each R^1 is independently selected from OH, $-(CH_2)_{1-4}OH$, $-CH_3-aF_a$, $-(CH_2)_{1-4}CH_3-aF_a$, $-OCH_3-aF_a$, halo, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, NO_2 , NH_2 , $-NH-C_{1-4}alkyl$, $-N-di-(C_{1-4}alkyl)$, CN, formyl, phenyl or heterocyclyl optionally substituted by $C_{1-6}alkyl$;

each R^2 is the group $Y-X-$

10 wherein each X is a linker independently selected from:

$-Z-$, $-O-Z-$, $-O-Z-O-Z-$, $-C(O)O-Z-$, $-OC(O)-Z-$, $-S-Z-$, $-SO-Z-$, $-SO_2-Z-$, $-N(R^7)-Z-$, $-N(R^7)SO_2-Z-$, $-SO_2N(R^7)-Z-$, $-(CH_2)_{1-4}-$, $-CH=CH-Z-$, $-C\equiv C-Z-$, $-N(R^7)CO-Z-$, $-CON(R^7)-Z-$, $-C(O)N(R^7)S(O)_2-Z-$, $-S(O)_2N(R^7)C(O)-Z-$, $-C(O)-Z-$ or a direct bond;

15 each Z is independently a direct bond, $C_{2-6}alkenylene$ or a group of the formula $-(CH_2)_p-C(R^7)_2-(CH_2)_q-$;

each Y is independently selected from aryl- Z^1- , heterocyclyl- Z^1- ,

$C_{3-7}cycloalkyl-Z^1-$, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $-(CH_2)_{1-4}CH_3-aF_a$ or $-CH(OH)CH_3-aF_a$; wherein each Y is independently optionally substituted by

20 up to 3 R^4 groups;

each R^4 is independently selected from halo, $-CH_3-aF_a$, CN, NO_2 , NH_2 ,

$C_{1-6}alkyl$, $-OC_{1-6}alkyl$, $-COOH$, $-C(O)OC_{1-6}alkyl$, OH or phenyl optionally substituted by $C_{1-6}alkyl$ or $-C(O)OC_{1-6}alkyl$,

or R^5-X^1- , where X^1 is independently as defined in X above and R^5 is

25 selected from hydrogen, $C_{1-6}alkyl$, $-CH_3-aF_a$, phenyl, naphthyl, heterocyclyl or $C_{3-7}cycloalkyl$; and R^5 is optionally substituted by halo, $C_{1-6}alkyl$, $-CH_3-aF_a$, CN, NO_2 , NH_2 , $COOH$, or $-C(O)OC_{1-6}alkyl$, wherein each phenyl, naphthyl or heterocyclyl ring in R^5 is optionally substituted by halo, CH_3-aF_a , CN, NO_2 , NH_2 , $C_{1-6}alkyl$, $-OC_{1-6}alkyl$,

30 $COOH$, $-C(O)OC_{1-6}alkyl$ or OH;

each Z^1 is independently a direct bond, $C_{2-6}alkenylene$ or a group of the formula $-(CH_2)_p-C(R^6)_2-(CH_2)_q-$;

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R^3 is selected from hydrogen, C_{1-6} alkyl or NHR^6 ;

R^6 is selected from hydrogen, C_{1-6} alkyl, OC_{1-6} alkyl, SO_2C_{1-6} alkyl, $(CH_2)_{0-3}OH$;

R^7 is independently selected from hydrogen, C_{1-6} alkyl or $-C_{2-4}$ alkyl- $O-C_{1-4}$ alkyl;

each a is independently 1, 2 or 3;

5 p is an integer between 0 and 2;

q is an integer between 0 and 2;

and $p + q < 4$.

with the proviso that:

- (i) when m is 1 or 2 and n is 0, R^3 is OH or $-O-C_{1-6}$ alkyl, then R^1 is other than OH, CN,
 10 halo, methyl, amino or nitro;
- (ii) when $m = 0$, $n = 1$, X is $-O-$, $-O-C(O)-$, $-S-$, $-S(O)-$, $-S(O_2)-$, $-N(CH_3)-$, $-N(CH_3)-CH_2-$ or $-C(O)-NH-$, R^3 is OH or $-O-C_{1-6}$ alkyl, then Y cannot be C_{1-6} alkyl or C_{1-6} alkyl substituted by C_{1-6} alkyl;
- (iii) when m is 0 or m is 1 and R^1 is NO_2 , R^3 is OH or $-O-C_{1-6}$ alkyl, then when n is 2
 15 $(R^2)_n$ cannot be di- C_{1-6} alkyl- $O-$ or C_{1-6} alkyl- $O-C_{1-6}$ alkenyl- $O-$ and when n is 3 $(R^2)_n$ cannot be tri- C_{1-6} alkyl- $O-$;
- (iv) when A is pyridyl, m is 0 or m is 1 and R^1 is halo, n is 1 and R^2 is phenyl, phenyl- CH_2-O- or pyridyl- $NH-$, then R^3 cannot be OH or $-O-C_{1-6}$ alkyl; and
- (v) when A is pyridyl, R^3 is OH, m is 0, n is 2 and one of the R^2 groups is
 20 phenyl- CH_2-O- , then the other R^2 group must be other than CH_3-S- or CH_3-SO_2- .

4. A compound according to claim 3 wherein m is 0 or 1 and n is 1 or 2.

5. A compound according to claim 4 wherein $n + m$ is 2 and the R^1 and/or R^2 groups
 25 are substituted at the 2- and 5- positions.

6. A compound according to any one of claims 3 to 5 wherein each R^1 is independently selected from OH, $CH_{3-a}F_a$, $OCH_{3-a}F_a$, halo, C_{1-6} alkyl, NO_2 or heterocyclyl optionally substituted by C_{1-6} alkyl.

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7. A compound according to any one of claims 3 to 6 wherein each R^2 is the group $Y-X-$, each X is independently selected from $-O-Z-$, $-C(O)O-Z-$, $-S-Z-$, $-SO-Z-$,

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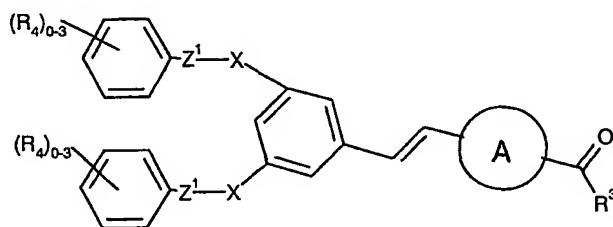
-SO₂-Z-, -N(R⁶)SO₂-Z-, -SO₂NH-Z-, -(CH₂)₁₋₄-, -CH=CH-Z-, -C≡C-Z-, -N(R⁶)CO-Z-, -CON(R⁶)-Z- or a direct bond, each Y is independently selected from aryl-Z¹-, heterocyclyl-Z¹-, C₃₋₇ cycloalkyl-Z¹-, C₁₋₆ alkyl, C₁₋₆alkoxy, C₂₋₆alkenyl or -CH(OH)CH_{3-a}F_a and each Y is independently optionally substituted by R⁴.

5

8. A compound according to any one of claims 3 to 7 wherein each R⁴ is independently selected from halo, -CH_{3-a}F_a, -OCH_{3-a}F_a, CN, NO₂, C₁₋₆alkyl, C₁₋₆alkoxy, -COOH, -(CH₂)₁₋₃COOH, -(CH₂)₀₋₃COOH, -C(O)phenyl, -C(O)NH₂, -C(O)NH-phenyl, -SO₂NH₂, -SO₂C₁₋₆alkyl, phenyl optionally substituted by C₁₋₆alkyl or -C(O)OC₁₋₆alkyl.

10

9. A compound of Formula (II)

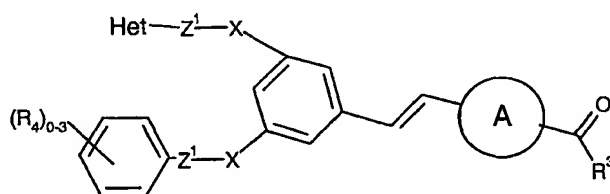


Formula (II)

wherein:

- 15 A, X, Z¹, R³ and R⁴ are as defined in claim 3;
or a salt, solvate or pro-drug thereof.

10. A compound of Formula (IIa)



Formula (IIa)

20

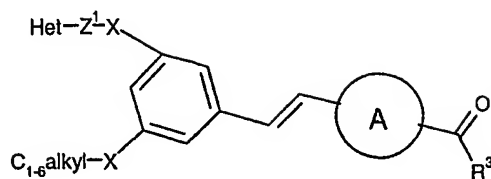
wherein:

Het is a monocyclic heterocyclyl, optionally substituted with between 1 and 3 groups selected from R⁴ and,

A, X, Z¹, R³ and R⁴ are as defined in claim 3;

- 25 or a salt, solvate or pro-drug thereof.

11. A compound of Formula (IIf)



Formula (IIf)

5 wherein:

Het is a monocyclic heterocyclyl,

the Het and C₁₋₆alkyl groups are independently optionally substituted with between
1 and 3 groups selected from R⁴,

the C₁₋₆alkyl group optionally contains a double bond, and

10 A, X, Z, R³ and R⁴ are as defined in claim 3;

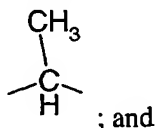
or a salt, solvate or pro-drug thereof.

12. A compound according to any one of claims 9 to 11 wherein:

X is independently selected from: -O-Z-, SO₂N(R⁶)-Z- or -N(R⁶)-Z-;

15 Z is a direct bond or -CH₂-;

Z¹ is selected from a direct bond, -CH₂- (CH₂)₂- or



; and

R³ is as defined above in a compound of Formula (I);

or a salt, solvate or pro-drug thereof.

20

13. A compound according to any one of claims 3 to 12 wherein A is selected from: pyridyl, pyrimidinyl, pyrazinyl, furanyl or thiazolyl.

- 25 13. A pharmaceutical composition comprising a compound according to any one of claims 3 to 13, or a salt, solvate or prodrug thereof, together with a pharmaceutically-acceptable diluent or carrier.

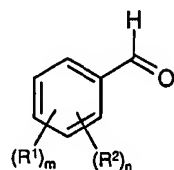
14. The use of a compound of Formula (I) or a salt, pro-drug or solvate thereof, as defined in claim 1, as a medicament,

with the proviso that:

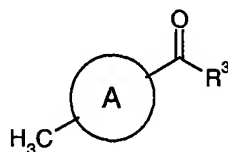
- (i) when A is pyridyl or thiazolyl, m is 1 or 2 and n is 0, R³ is OH or -O-C₁₋₆alkyl, then R¹ is other than halo, amino or nitro;
- (ii) when A is pyridyl, m = 0, n = 1, X is -N(CH₃)- or -N(CH₃)-CH₂-, R³ is OH, then Y cannot be methyl;
- (iii) when A is thiazolyl, m is 0, R³ is OH, then when n is 2 (R²)_n cannot be di-C₁₋₆alkyl-O- or C₁₋₆alkyl-O- C₁₋₆alkenyl-O- and when n is 3 (R²)_n cannot be tri-C₁₋₆alkyl-O-;
- (iv) when A is pyridyl, m is 0 or m is 1 and R¹ is halo, n is 1 and R² is phenyl-CH₂O-, then R³ cannot be OH; and
- (v) when A is pyridyl, R³ is OH, m is 0, n is 2 and one of the R² groups is phenyl-CH₂O-, then the other R² group must be other than CH₃-S- or CH₃-SO₂-.

15 15 A process for the preparation of a compound of Formula (I) which comprises:

(a) reaction of a compound of Formula (IIIa) with a compound of Formula (IIIb),

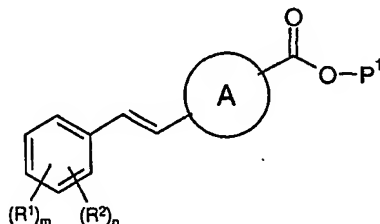


Formula (IIIa)



Formula (IIIb);

(b) for compounds of Formula (I) wherein R³ is hydrogen, de-protection of a compound of Formula (IIIc),



Formula (IIIc)

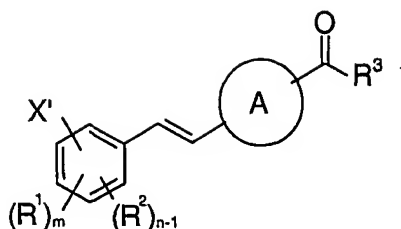
wherein P¹ is a protecting group;

(c) reaction of a compound of Formula (IIId) with a compound of Formula (IIIe),

- 75 -



Formula (III d)



Formula (III e)

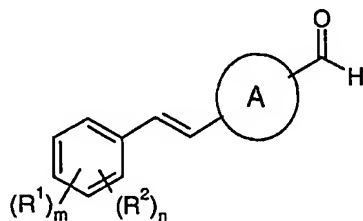
wherein X' and X'' comprises groups which when reacted together form the group X ;

(d) for a compound of Formula (I) wherein X or X^1 is $-SO-Z-$ or $-SO_2-Z-$, oxidation of the

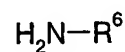
5 corresponding compound of Formula (I) wherein X or X^1 respectively is $-S-Z-$; or

(e) for a compound of Formula (I) wherein R^3 is NHR^6 , reaction of a compound of

Formula (III f) with a compound of Formula (III g),



Formula (III f)



Formula (III g);

10 and thereafter, if necessary:

i) converting a compound of Formula (I) into another compound of Formula (I);

ii) removing any protecting groups;

iii) forming a salt, pro-drug or solvate thereof.

15 16. The use of a GLK activator in the preparation of a medicament for the combined treatment or prevention of diabetes and obesity.

17. The use of a GLK activator as defined in Claim 16 wherein the GLK activator is selected from a compound of Formula (I) as defined in Claim 1.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/02903

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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A	BELLER ET AL: "Photochemical Synthesis of Benzo 'f' quinolines" J.ORG.CHEM., vol. 42, no. 22, 12 April 1977 (1977-04-12), pages 3514-18, XP001095960 7d-7g page 3515; examples 7D-7G ---	3
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